MARCH, 1952

The Review of Gastroenterology

OFFICIAL PUBLICATION

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

SYMPOSIUM ON THE PANCREAS

The Pathological Aspects of Pancreatic Disease

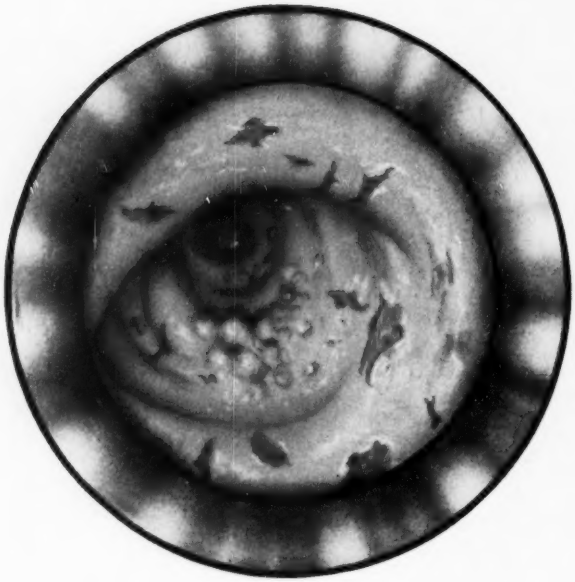
Diseases of the Pancreas: Medical Aspects

Surgical Aspects of Pancreatic Disease

•

Seventeenth Annual Convention
New York, N. Y., 20, 21, 22 October 1952

VOLUME 19 NUMBER 3



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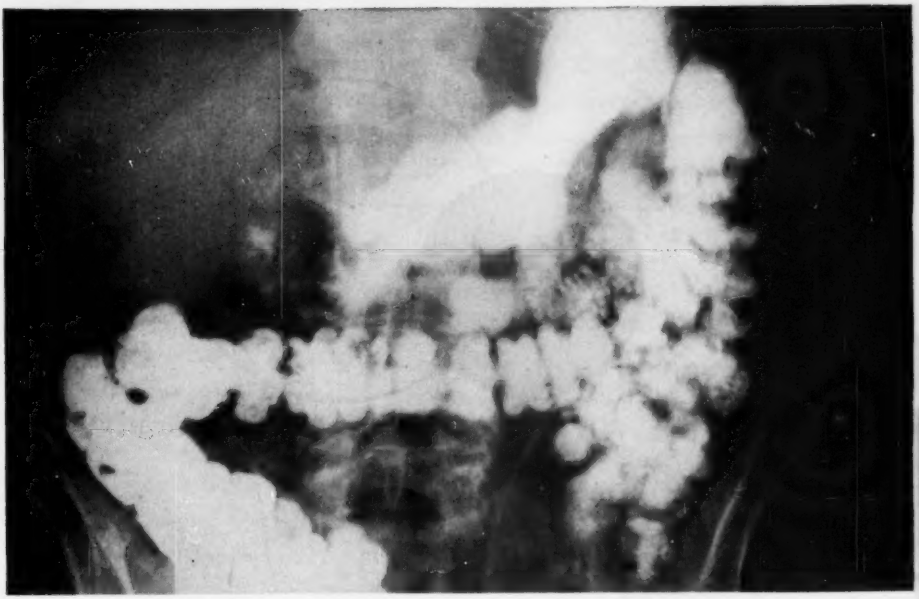

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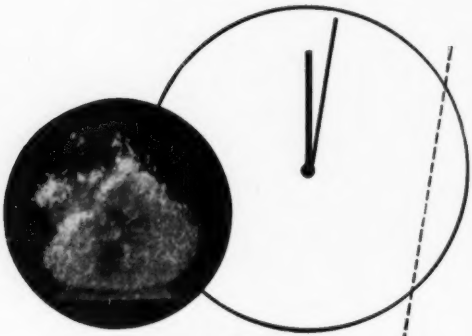

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(INCORPORATING THE AMERICAN JOURNAL OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

VOLUME 19 MARCH, 1952 NUMBER 3

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2. Sandweiss, D. J.: The Present-Day Treatment of Duodenal Ulcer, Pennsylvania M. J. *52*:1543, 1949.
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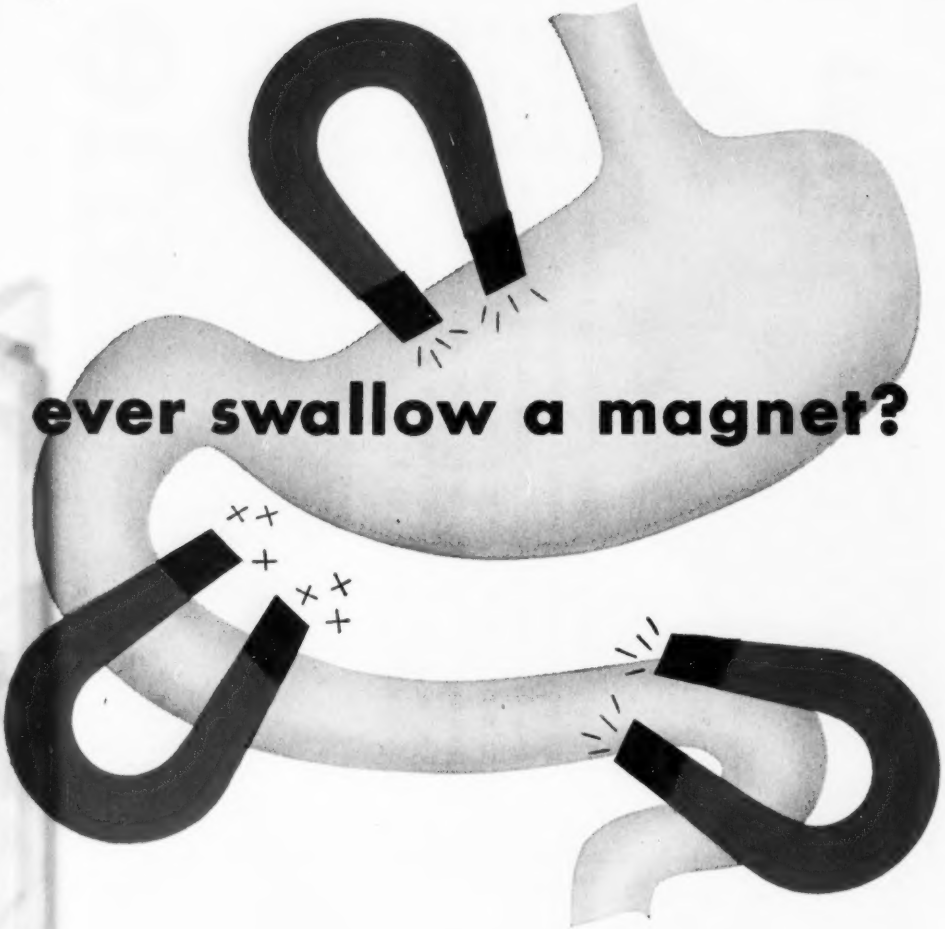

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2 Marks, J.: Review of Gastroenterology **16**:82 (Jan.) 1949.
3 Weiss, J.: Review of Gastroenterology **15**:826 (Nov.) 1948.
4 Wilkinson, J., and Martin, J.: Physical-Chemical Aspects of the Action of Anion Exchange Resins in Biochemical System. Arch. Biochem. **10**:205, 1946.

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Volume 19 MARCH, 1952 Number 3

SYMPOSIUM ON THE PANCREAS

THE PATHOLOGICAL ASPECTS OF PANCREATIC DISEASE*

HANS POPPER, M.D., Ph.D.†

Chicago, Ill.

In recent years, experiences with experimental animals as well as on the autopsy table have changed somewhat our concepts of pancreatic diseases. This holds true, especially for the inflammation and degeneration of the exocrine part of the pancreas to which topic the following discussion is restricted.

Degenerations and inflammations specific for the exocrine parenchyma of the pancreas and not due to factors operating in other organs are mainly related to abnormalities of secretion, activation and flow of the enzymes which are formed by the acinar cells of the pancreas and are drained through its ductal system. These abnormalities are the basis of the pathogenesis as well as the laboratory diagnosis of pancreatic disease. The pancreas is the organ which forms the greatest amount of protein per unit weight as determined, for instance, with radioactive methionine; the greatest amount of an administered test dose is stored in the pancreas[1]. The protein which the pancreas produces is, to the greatest extent, enzyme protein. The production of such large amounts of protein by the pancreas makes it especially susceptible to protein deficiency when lack of raw material interferes with enzyme formation. Such a deficiency is aggravated by a high-caloric diet poor in protein, e.g., a predominantly carbohydrate diet.

In the malignant type of malnutrition, which commonly occurs in tropical areas and which is often designated as Kwashiorkor[2,3], pancreatic atrophy is encountered[4]. Davies[4] considers this atrophy the result of demands on the pancreas occurring in childhood when, immediately after weaning, a high caloric

*Read before the Sixteenth Annual Convention of the National Gastroenterological Association, Chicago, Ill., 17, 18, 19 September 1951.

†Associate Professor of Pathology, Northwestern University; Scientific Director, Hektoen Institute for Medical Research; Director, Department of Pathology, Cook County Hospital, Chicago, Illinois.

diet is given consisting mainly of carbohydrates, protein being deficient or poor in biological quality. Hepatic changes like fatty liver may be secondary to the pancreatic lesion. Similar observations were made in infants in the West Indies[6] and in Hungary[5] who were on diets poor in animal protein because of economic conditions or during a famine. Atrophic and inflammatory lesions associated with acute necrosis, interstitial infiltration and cyst formation have also been observed in the pancreas of experimental animals which have been subjected to various modifications of a low protein-high fat diet[7,8,9]. Administration of methionine or caseine exerted a protective effect[5]. In malnutrition produced by diseases, pancreatic alterations have also been reported such as in chronic ulcerative colitis[10] or in hepatic cirrhosis[11]. Recently, we have been impressed by the common occurrence of fat droplets in the pancreatic acinar cells in patients with cirrhosis or fatty liver.

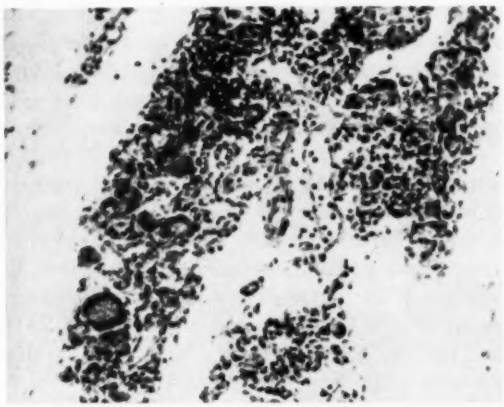

Fig. 1—(230 x) Chronic pancreatic atrophy in a rat which had been for 28 days on a diet containing ethionine. The acini are atrophic, the fibrosed interstitial connective tissue is infiltrated by lymphocytes and histiocytes. (Studies with Dr. Dieter Koch-Weser).

The close relation between available protein and pancreatitis has been experimentally well illustrated by experiences of Farber in our laboratory[12] with ethionine which is an analogue to methionine, probably antagonistic to it in some phases of the metabolism. It inhibits the incorporation of radioactive methionine into the proteins of some tissues *in vivo*[13,14] and, therefore, is assumed to inhibit protein synthesis. After administration of ethionine, rats revealed within 24 hours a loss of the cytoplasmic basophilia of the acinar cells. This basophilia is caused by the presence of nucleic acids in the cytoplasm and is therefore considered to indicate the site of protein formation[15]. Subsequently, an interstitial inflammation develops associated with necrosis of pancreatic acini and fat. This lesion can be entirely prevented by the administration of methionine and was thus considered a result of interference of ethionine with methio-

nine and possibly protein metabolism. The same findings were then reported by others[16] and confirmed[17]. In dogs a similar lesion was produced[18]. Recently, we have noted a chronic interstitial pancreatitis with atrophy of the acini as a result of feeding ethionine for 4 weeks[19] (Fig. 1). These observations raise the question as to whether or not human malnutrition and, specifically, protein deficiency, may play a role in pancreatic disorders, especially from the point of view of interfering with enzyme formation.

The main pancreatic enzymes are 1) amylase, which splits starch and glycogen to maltose; 2) lipase, which emulsifies and splits fats to fatty acids and glycerols (to this group belong also the esterases, e.g., the one splitting choline from lecithin); 3) trypsinogen (including chymotrypsinogen) which after being activated to the respective trypsin by enterokinase (formed in the intestinal mucosa[20]), splits proteins to peptones and peptides and further down to amino acids with the help of peptidases formed in the pancreas and intestinal mucosa. This activation is not only brought about by the enterokinase of the intestinal mucosa, but also by bile, bacteria, active trypsin and even spontaneously[21]. The enzyme formation is stimulated by foods which probably stimulate specifically the respective enzymes[22]. In addition, alcohol and acids are strong stimulants. It is customary to differentiate between a stimulation which results mainly in an increased secretion of water and bicarbonate but not of the amount of enzymes produced per minute ("hydrelatic") and the increased production of enzymes themselves ("ecbolic"[22]). The strongest hydrelatic stimulus is secretin formed and released by the mucosa of the upper small intestine[20]. Ecbolic stimuli are probably the hormone pancreozymin (also released from the mucosa of the upper small intestine under the influence of various foodstuffs[20]); furthermore, the act of eating itself (cephalic stimulation), vagus stimulation in general and specifically, administration of mecholyl chloride.

The escape of the enzymes from their normal channels as well as their premature activation before entering the intestine are basic processes in pancreatic diseases. Trypsinogen, after being activated to trypsin and escaping into the interstitial tissue of the pancreas, digests the pancreatic tissue as well as the vessels and thus leads to hemorrhage (Fig. 2a). Activation alone without escape seems not to produce the lesion[21]. Lipase escaping into the interstitial tissue, either due to rupture of the acini or due to preceding digestion, splits fats in the interstitial and fat tissue to glycerol and fatty acids, the latter combining with calcium salts, a process called fat necrosis (Fig 2b). This process leads to an escape of the enzyme into the general circulation, mainly through the portal vein[23], mirrored in a rise of the serum lipase[1] as well as to a reduction of the serum calcium level[24], the latter occasionally being depressed enough to produce tetany[25]. The escape of amylase as a result of similar processes leads to its rise in the serum beyond the amounts of amylase normally present in serum and probably not of pancreatic origin. It appears thus that escape of enzymes from

the acinar lumen (usually associated with activation) results in changes which, if of lesser degree, represent interstitial or edematous pancreatitis and if more severe, necrosis and hemorrhage. Although in principle the pathogenesis of the acute pancreatic degeneration and necrosis (customary but not always justifiably called pancreatitis) is well understood, the cause of the spontaneous acute pancreatic necrosis or pancreatitis, especially if extensive, is still moot. Several factors can be listed as possible causes of this clinically alarming condition:

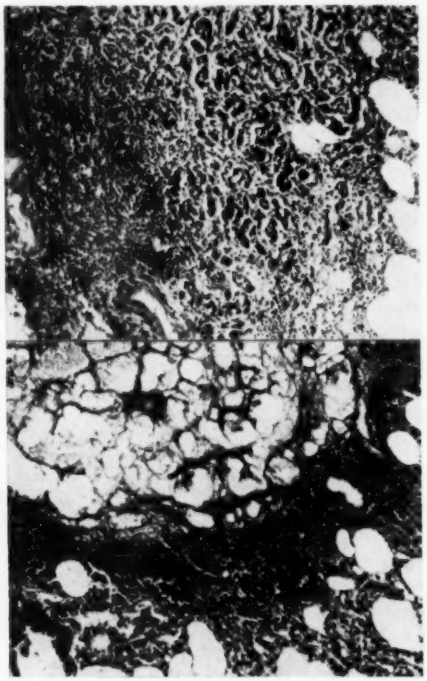

Fig. 2—A. (Top) (130 x) Digestion of pancreatic parenchyma and vessels in acute pancreatitis. The necrotic zone is demarcated by segmented leucocytes.
B. (Bottom) (130 x) Fat necrosis with calcium deposition in acute pancreatitis.

1. Bile regurgitation from the bile ducts through a common channel[26] past the obstructed papilla of Vater, into the pancreatic ducts. This possibility was strongly suggested by the classical observation of Opie who found in a case of acute pancreatitis a stone lodged in the papilla of Vater[27] and by the radiologic demonstration of pancreatico-biliary reflux[28]. The possibility of such an etiology of acute pancreatitis depends upon two factors: (a) the anatomy of the junction of the common and pancreatic ducts; with independent openings a common channel is impossible; but even when the two ducts have a common ampulla, it

has to be of sufficient length to permit a common channel. The literature reveals much disagreement as to the length required and the figures reported from examination of anatomic specimens as to the possibility of a common channel vary between 36 and 71 per cent[28,29]. (b) obstruction of a common opening at the papilla of Vater by either a stone or by sphincter of Oddi spasm; anatomical evidence for such an occurrence is not easily obtainable; it can be found in far less than 10 per cent of all instances of acute pancreatitis. In a significant number of cases independent opening of common and pancreatic duct was demonstrable (Fig. 3). It is, therefore, agreed that regurgitation of bile cannot be the general cause of acute pancreatitis[30,31].

2. Infection has been considered but is rarely demonstrable.

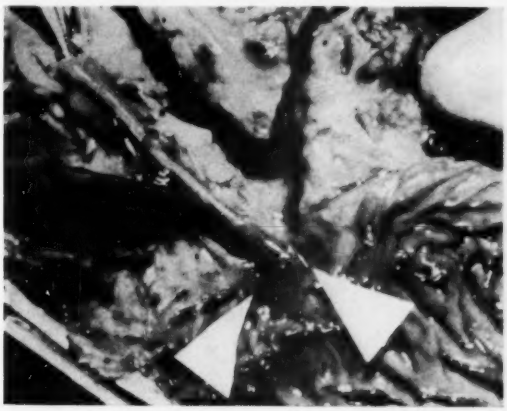

Fig. 3—Independent opening of common and pancreatic ducts at the papilla of Vater in a case of acute hemorrhagic pancreatitis.

3. Squamous metaplasia of the pancreatic ducts[30] obstructing their lumen has been mentioned but was not found regularly in our material.

4. Arterial occlusion[32] as brought about e.g., by arteriolosclerosis or periarteritis nodosa frequently produces lesions but they are focal and not the cause of extensive changes.

5. Trauma[33] may produce focal fat and pancreatic necrosis, e.g., after abdominal surgery, but it does not account for the majority of the instances of extensive pancreatic necrosis.

6. Excessive stimulation of enzyme secretion[1] as for instance brought on by a heavy meal, is a likely cause and the first symptoms appear often after such a meal. This is supported by the experimental production of acute pancreatitis

by prolonged daily administration of mecholyl[34] which produces both stimulation and obstruction.

7. Abuse of alcohol[35], acute or chronic, is recognized as a common cause of pancreatitis. A large number of our own cases gave a history of alcoholism. The relation may either be stimulation of pancreatic secretion by alcohol or the associated malnutrition in view of the previously reported experimental findings in protein deficiency.

8. Local obstruction of small ducts in chronic relapsing pancreatitis. Since evidence of chronic pancreatic changes is found in a significant number of cases of acute pancreatitis, this possibility is to be strongly considered.

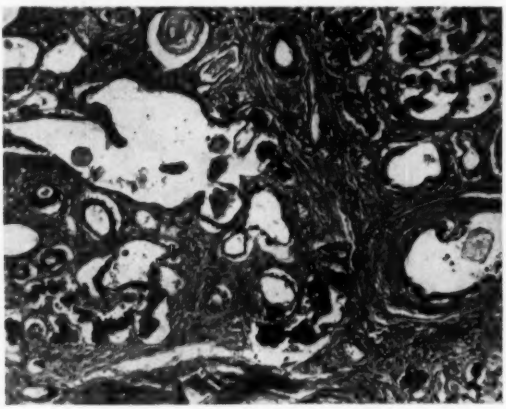

Fig. 4—(105 x) Fibrocystic disease of the pancreas in infant. Dilatation of ducts and acini, both containing inspissated material; proliferation of cells, transitional between acinar and island cells. Extensive interstitial fibrosis.

Concluding, the main etiologic factors of acute diffuse pancreatic necrosis are protein deficiency, excessive enzyme stimulation and obstruction of either the main pancreatic duct or of multiple small ducts. A combination of these factors may play an important role in the individual case.

Multiple obstructions in early infancy are considered the cause of a characteristic disease picture, fibrocystic disease of the pancreas (Fig. 4), in which dilatation of the smallest ducts and acini is associated with a diffuse fibrosis and proliferation of cells which represent a transition between acinar and insular cells. According to Farber[36], inspissated secretion[37] due to disturbance of the autonomous nervous stimulation of glandular secretion in the pancreas (and/or elsewhere) is the underlying cause. However, congenital atresia of the ducts as an embryologic malformation still cannot be excluded (Baggenstoss).

In the adult, however, multiple obstructions are associated with the disease entity of chronic relapsing pancreatitis, the importance of which has recently been emphasized by clinical investigations by a group at the Mayo Clinic, which is represented here by Dr. Gambill[38,39]. This disease, which is not uncommon[40,41], escapes clinical recognition because of the misleading symptoms which the patient may exhibit. It is far more frequently diagnosed on the autopsy table than at the bedside[42]. It is characterized by a vicious circle in that small foci of acute

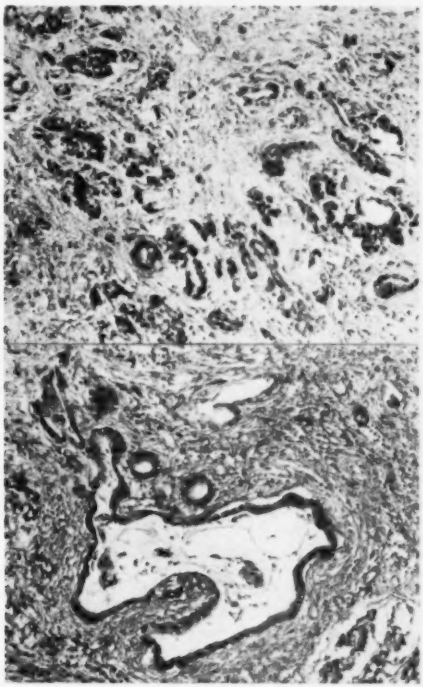

Fig. 5—Chronic relapsing pancreatitis.
A. (Top) (130 x) Extensive intra- and perilobular fibrosis with atrophy and distortion of the acinar cells.
B. (Bottom) (130 x) Distortion of a small pancreatic duct by scar tissue. Its lumen contains inspissated proteinic material.

pancreatitis caused by whatever reason lead to interstitial infiltration and intra- and perilobular fibrosis (Fig. 5a) of the pancreatic tissue which in turn causes kinking of the pancreatic ducts (Fig. 5b). The latter causes both obstruction producing added fibrosis or acute pancreatitis; furthermore dilatation of the ducts with hyperplasia of the ductal epithelium and accumulation of proteinic debris in the lumen. Calcium salts may be deposited into this debris with resulting calculus formation representing an additional cause for acute pancreatitis of

variable degree. The acute pancreatic foci may lead to either a continuation of the vicious circle or, sometimes, to severe extensive (often hemorrhagic) pancreatitis resulting in abscess or cyst formation or in fatal outcome. Pancreatic lithiasis or calcification[43,44,45] is usually secondary to chronic relapsing pancreatitis and only occasionally primary. As Edmondson et al[46] point out, the fact that the pancreatic juice is supersaturated with calcium predisposes the calcium deposition into the stagnating proteinic debris. The initial cause of the vicious circle of chronic relapsing pancreatitis is still not fully established. Alcholism plays an important role, accounting for at least 40 per cent of the cases[42]. Episodes of protein deficiency may be significant. The common association with biliary tract disease appears important[39,47] pointing again to the possibility of a biliary-pancreatic reflux. On the other hand, the possibility of liver disease being an etiologic factor is suggested by the common occurrence of minor pancreatic alterations in patients with primary liver diseases.

Chronic relapsing pancreatitis leads to a series of sequelae well analyzed in the studies of Gambill and his co-workers[38,39]. These are: 1) involvement of the common duct causing dysknesia and cholecystitis which were found in about 50 per cent of their cases. These observations are supported by experimental studies[48]; the common duct involvement, is in some instances, severe enough to even produce obstructive jaundice. 2) Hepatic involvement due to defective intestinal absorption of protein[52] or of the lipotropic substance, choline, leading to fatty liver in acute and cirrhosis in chronic conditions[49,50,51]. 3) Involvement of the islands of Langerhans causing diabetes in about 20 per cent of the cases. 4) Steatorrhea occurring in about 20 per cent of the cases and resulting in malnutrition.

It should be stressed that chronic relapsing pancreatitis can be easily confused with carcinoma of the head of the pancreas, even at operation. We have one case on record in which the pancreas was removed at operation and diagnosed grossly and microscopically as chronic pancreatitis, while on thorough microscopic study it revealed a small cancer obstructing the common duct and inducing an apparently secondary chronic pancreatitis.

Deliberately, little was said about the carcinoma of the pancreas since not much can be added to recent analyses[53,54,55]. Recently the anatomic pathologist has entered the field of clinical diagnosis of carcinoma of the pancreas through the study of exfoliated pancreatic cancer cells in duodenal aspirations[56,57].

In closing, the importance of abnormalities of secretion, activation and flow of pancreatic enzymes was emphasized as the cause of acute and chronic pancreatitis. In the pathogenesis of the former, obstruction of the main duct as well as of multiple smaller ducts, of enzyme stimulation and of protein deficiency were stressed, the latter on the basis of the experimental production of pancrea-

titis by an amino acid antagonist, presumably inhibiting protein synthesis. The importance of chronic pancreatitis (itself the result of a vicious circle starting with acute pancreatitis) in the causation of extensive pancreatic necrosis was discussed.

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DISEASES OF THE PANCREAS: MEDICAL ASPECTS*

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Diseases of the pancreas may be classified into three main categories; namely, inflammatory, malignant, and deficiency types. This paper deals only with inflammatory and malignant diseases.

Certain difficulties exist in the recognition and study of pancreatic disease because the pancreas, not being a hollow viscus, is not subject to roentgenoscopic studies with barium. The number of laboratory tests that are specific for pancreatic function is limited, and the timing factor limits the value of the serum enzyme tests in the individual case. Furthermore, the location of the organ renders palpation difficult or impossible so that the physical examination often adds little or nothing which is specific for pancreatic disease. Consequently, one has to rely heavily on the clinical history in arriving at a diagnosis.

Inflammatory Conditions

Most inflammatory conditions of the pancreas are nonspecific and are recognized as the ordinary forms of acute and chronic, or chronic, relapsing pancreatitis. Pathologically, acute pancreatitis may range from pancreatic edema to pancreatic necrosis. "Relapsing" refers to repeated attacks of pancreatitis. Chronic pancreatitis is used with or without the word "relapsing" to refer to those cases in which, because of repeated attacks, chronic inflammatory changes develop in the pancreas, or in which there is chronic pain due to pancreatitis, or in which certain sequelae such as steatorrhea, diabetes mellitus or pancreatic cysts are presented[1]. It is likely that the different designations refer to variations in the severity and acuteness or chronicity of the same disease.

No consistent figures are available as to the incidence of pancreatitis. It appears to be more prevalent than formerly reported, probably owing to an improved index of suspicion by the medical profession.

The relapsing type is found much more commonly in men, the ratio of men to women being from 3 to 6 males to 1 female[1,2].

Relapsing pancreatitis tends to occur at an earlier age than cholecystic disease, most of the patients being in the fourth and fifth decades of life[1,2]. In one series of 29 cases my associates and I found that 34 per cent began having the attacks of pain prior to 30 years of age.

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*Read before the Sixteenth Annual Convention of the National Gastroenterological Association, Chicago, Ill., 17, 18, 19 September 1951.

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The cause of pancreatitis is not definitely known. There are likely multiple contributing factors such as alcoholism, gallstones, the effects of large greasy meals, and trauma over the pancreas, but the infectious element seems insignificant in most cases. The theory of regurgitation of bile and duodenal contents is the one most widely accepted. It may be that there is a certain element of choledochoduodenal dyskinesia peculiar to these individuals.

Symptoms:—The most important symptom of relapsing pancreatitis is the recurrent episodes of upper abdominal pain[1,2]. This pain can be relatively mild, may last only a few hours, and may involve any part of the abdomen. More often, however, it is severe, may be protracted for days and may require multiple hypodermic injections of morphine. It may spread from the upper to the lower part of the abdomen and around into the upper lumbar region of the back. At times it may be limited to the right upper part of the abdomen and corresponding level in the back, in which case it may be confused with gallstone colic. It may be referred to the anterior part of the chest and shoulder. The pain is most characteristic when it shifts to, or is primarily centered in, the left upper part of the abdomen. It is most often gradual in onset and cessation, tends to be steady, but there may be superimposed waves of exaggeration. The pain may be described as piercing, burning, colicky, cramping, cutting or boring.

The attacks often become increasingly frequent, severe and prolonged but the opposite may occur.

Occasionally patients experience, for a few hours or days prior to the attack, prodromal symptoms such as nausea, anorexia, weakness and flatulence.

Numerous symptoms accompany the pain such as nausea and vomiting, the latter sometimes affording partial and evanescent relief. Retention vomiting may occur due to duodenal obstruction or ileus. Generalized abdominal distention, the inability to belch or to pass flatus, and the feeling that all gastrointestinal activity ceases is common owing to adynamic ileus. The return of borborygmi and the passage of flatus may herald the cessation of pain. The entire abdomen is often tender, the tenderness being maximal in the upper part of the abdomen, so that coughing, sneezing, and turning in bed may be done with reluctance. Tenderness, anorexia and weakness may persist for days after cessation of pain. Obstipation is the rule.

In the intervals between the acute episodes patients may be symptom free or present varied complaints none of which are diagnostic of pancreatitis. Among these are flatulent dyspepsia, heartburn, vague epigastric pains and weakness.

Fatty, voluminous, malodorous stools characteristic of steatorrhea may be encountered, in which case loss of weight and strength is noted.

Physical Signs:—Between the attacks of pain there may be no physical signs, though epigastric tenderness is not rare. Pancreatic cysts are usually palpable. During the acute attack there is generalized abdominal tenderness of the direct and rebound type, muscle guarding and spasm maximal in the epigastrium. The swollen, tender pancreas can sometimes be felt lying transversely in the epigastrium. The more severe attacks may present findings suggesting generalized peritonitis with ileus, distention, tachycardia, fever, ascites and even mild shock. A dilated stomach with splashy contents may be demonstrated. The patient may lie quietly in bed, reluctant to move or breathe deeply, or he may sit up with trunk flexed and the arms folded tightly across the abdomen. Occasionally the liver and spleen may be enlarged and there may be mild icterus. High fever and chills are not characteristic.

Laboratory Aspects:—Only those laboratory findings which have a diagnostic bearing will be mentioned. The most valuable laboratory aid is the finding of increased concentration of amylase and lipase in the blood serum during the acute seizures. These values revert to normal soon after cessation of the pain. Increased values for these enzymes may not appear if the pancreas has been sufficiently damaged.

During the attack a mild degree of hyperbilirubinemia may appear. In the presence of fat necrosis the concentration of calcium in the serum may be decreased. This may be a prognostic aid, according to Edmondson and Berne[3], who have said that values of less than 7 mg. per 100 c.c. of serum are usually followed by death. In a case of fatal pancreatitis observed by my colleagues and myself[4], the concentration of serum calcium was 5.5 mg. per 100 c.c. At necropsy tremendous amounts of calcium and phosphorus were present in the sites of fat necrosis inside and outside the pancreas.

Glycosuria may appear in some instances of pancreatitis and may be temporary or permanent. Steatorrhea, suspected in the presence of voluminous, greasy, malodorous stools, may be confirmed by chemical determination of the fat content of the stool—preferably by using a twenty-four to forty-eight hour specimen collected while the patient's diet contains 100 gm. of fat.

While the secretin test may be useful in detecting deficiency of external pancreatic secretion, its use is not often necessary for the diagnosis of pancreatitis.

The fasting gastric contents may be abnormally high in acute pancreatitis owing to duodenal obstruction or to ileus.

A simple roentgenogram of the abdomen may disclose calcific deposits, either localized or diffuse, in the pancreatic region. Cholecystograms taken soon

after an attack of pancreatitis may reveal no function or poor function of the gallbladder due to cholecystic disease, or pancreatitis, or both. Roentgenologic studies of the stomach and duodenum made with the aid of barium may reveal gastric dilatation, widening of the duodenal loop, hypomotility and even ulcer-like deformities of the duodenum, the result of adhesions or pressure.

Complications:—Pancreatic calcification may appear in perhaps a third to a half of the cases of relapsing pancreatitis[1,2,5]. This has been observed as early as a year and as late as ten to twenty years after the first episode of pain[5]. The extent of calcification does not necessarily parallel the severity of the disease, since there may be extensive calcification without any evidence of disturbed pancreatic function[5]. However, pancreatic steatorrhea and diabetes mellitus are much more common in pancreatitis with calcification than in pancreatitis without calcification[5].

Diabetes mellitus has been observed in 15 to 20 per cent of cases of relapsing pancreatitis[1,2].

Steatorrhea may occur as an eventual complication in 25 to 30 per cent of cases, and it may be associated with considerable loss of weight[1,2].

Inflammatory pseudocysts of the pancreas have been observed in 10 to 15 per cent of individuals with relapsing pancreatitis[1,2]. These cysts may be single or multiple and often contain high concentrations of pancreatic enzymes.

Diagnosis:—As in other diseases, the first prerequisite to the diagnosis of pancreatitis is to think of the possibility. If the history is sufficiently typical, an accurate diagnosis can often be presumed on that basis alone. Actual proof of the diagnosis will rest on demonstration of increased concentration of enzymes in the serum or of disturbances in pancreatic function, or on examination of pancreatic tissue.

The following criteria are useful in the diagnosis of relapsing pancreatitis. A history of recurrent attacks of severe pain in the upper part of the abdomen during the course of which steatorrhea, diabetes mellitus, or pancreatic calcification develops is strong evidence for pancreatitis, provided antecedent diabetes and other causes for steatorrhea can be excluded.

In the absence of these complications the diagnosis has to be made on the basis of the recurrent nature of the attacks, the severe and prolonged pain, the exclusion of other causes for pain and the finding of increased concentration of lipase or amylase in the serum. The chief conditions which must be differentiated are acute myocardial infarction, acute cholecystitis and its complications, acute perforation of a viscus, such as from gastric or duodenal ulcer, with peritonitis, thrombosis of the mesenteric vessels and acute intestinal obstruction.

Pancreatitis is most difficult to diagnose when the attacks are relatively mild, when the pain is in an atypical location and when there are no evidences of complications. The recurrent nature of the attacks and the finding of increased concentration of pancreatic enzymes in the serum during an acute attack lead one to the correct diagnosis. The concentration of enzymes is not increased if the pancreas is severely damaged. Occasionally false elevation of values for serum enzymes may occur after injection of opiates or in the presence of a perforated peptic ulcer.

The policy of suspecting pancreatitis in anyone suffering from recurrent attacks of epigastric pain and of obtaining a sample of blood for determination of serum amylase and lipase during or soon after the attack should result in the more frequent recognition of the disease.

Treatment:—The treatment of pancreatitis is far from satisfactory. I shall discuss only the medical aspects of treatment. These are limited to efforts to reduce insults to the pancreas, and to the treatment of the acute attacks and complications.

Alcoholic beverages and large, greasy meals are interdicted. For the acute attack opiates and other drugs are given to control pain. Gastric and intestinal aspirations are employed for gastric retention and ileus. Dehydration, nutritional deficiency and electrolytic imbalance are treated by intravenous use of glucose, sodium chloride, ammonium chloride, sodium lactate, vitamins and amino acids as indicated. Diabetes and steatorrhea are treated by replacement therapy with insulin and pancreatin, respectively, as indicated. Pancreatin in doses of 2 to 10 gm. three times daily helps to control the steatorrhea. Drugs to reduce pancreatic secretion and choledochoduodenal spasm, such as methantheline (banthine), ephedrine, and atropine, are worth trying.

Malignant Lesions of the Pancreas

Carcinoma of the pancreas is encountered fairly often by the clinician.

In a study of 202 cases of primary carcinoma in which necropsy was performed at the Mayo Clinic during the years 1920 through 1945, Miller and coworkers[6] noted involvement of the head of the pancreas in 71 per cent and of the body of the pancreas in 29 per cent. In 61 per cent of the cases the malignancy was graded 3 or 4 (on a basis of 1 to 4 in which 1 is the least and 4 is the most malignant). Males were affected two and a half times more often than females. Most patients were in the sixth and seventh decades of life.

Carcinoma of the pancreas often appears in previously well individuals. The symptomatology is influenced somewhat by the location of the lesion, the rapidity and extension of growth, the presence or absence of metastasis and the

presence of complications. Lesions in the head of the pancreas may produce symptoms that lead to a correct diagnosis earlier than those which start in the body of the pancreas. Thus, it often happens that by the time carcinoma of the body of the pancreas is recognized, extensive metastasis has already occurred.

Jaundice is usually an early and common symptom in lesions of the head of the pancreas. It is often but not always painless, progressive and intense. It may be the result of organic obstruction of the common bile duct or, as Drapiewski[7] has pointed out, it may be due to a physiologic block, the common duct being found patent at examination in 46 per cent of 83 cases studied by him at necropsy. Part of the jaundice may be due to hepatic metastasis.

Pain is less frequent in lesions of the head than of the body and tail of the pancreas. Occasionally a biliary colic type of pain is noted but the usual type, particularly in lesions of the body, is the constant, progressive, relentless pain located around the upper part of the abdomen and upper lumbar region of the back in a bandlike distribution. Pain may be described as boring, grinding, burning or aching, and is characteristically worse in recumbency so that it tends to interfere with sleep. While it usually begins across the epigastrium, it may start first in the upper lumbar portion of the back, or it may even start in the lower part of the abdomen and later move into the epigastrium and back. Perhaps the most suggestive feature is its aggravation in recumbency. Rarely, pain is essentially absent, even late in the disease. In many cases it is the most disabling and hardest aspect of the disease to treat. Metastasis to the perineural lymph spaces is common, which helps explain the constant and severe pain.

Weakness, loss of weight and anorexia occur often and are rapid in development. In lesions of the head of the pancreas pruritus often is present.

Gaseous dyspepsia, anorexia, bloating and constipation are prominent, but diarrhea may occur. Nausea and vomiting may take place. Hematemesis, melena, chills and fever are rare. Mental depression may develop.

Venous thrombosis is encountered fairly often, being observed in 29 per cent of the series studied by Miller and associates[6]. This finding is more common in malignancy of the body than in malignancy of the head of the pancreas[6], possibly owing in part to the high incidence of metastasis associated with lesions of the body of the pancreas.

The passage of dark urine and light-colored stools is among the earliest symptoms in lesions of the head of the pancreas.

Physical Signs:—Jaundice is an early sign in carcinoma of the head and a late sign in a lesion of the body of the pancreas. It is usually rapidly progressive and intense.

A palpable, distended gallbladder may be found in perhaps 40 to 50 per cent of the cases in which the carcinoma is in the head of the pancreas.

The liver is commonly enlarged, and may or may not feel nodular.

The posture which the patient assumes in an effort to gain some relief has been a most helpful and reliable outward sign of carcinoma of the body of the pancreas. Typically, the patient is often found sitting up with trunk flexed, or lying on either side with the thighs drawn up tightly against the abdomen.

Gaseous distention of the abdomen is often observed. Ascites is uncommon. Pruritic marks and mental depression may be observed.

Laboratory Findings:—The concentration of bilirubin in the serum is usually moderately to markedly increased in lesions of the head but often is normal or nearly so in lesions of the body of the pancreas.

The concentration of serum lipase and amylase may be increased in some individuals, usually in lesions of the head of the pancreas. This is thought to be due largely to obstruction of the pancreatic duct, but can be produced by an associated pancreatitis.

The concentration of total cholesterol in the plasma and of alkaline phosphatase in the serum may be elevated. The prothrombin time (Quick) may be prolonged, but if such prolongation is due merely to lack of bile in the intestinal tract and not to metastasis, the prothrombin time promptly returns to normal after the administration of water-soluble Vitamin K.

Whenever the lesion involves the tail of the pancreas the fasting blood sugar may be increased above normal.

The value for hemoglobin, the leucocyte and erythrocyte counts and the sedimentation rate may often be essentially normal.

Sometimes retention of sulfobromophthalein may be the only positive laboratory sign in lesions of the body of the pancreas.

Roentgenologic studies made with the aid of barium may reveal enlargement, dilatation and widening of the duodenal loop or displacement of the stomach.

Cholecystograms in the presence of carcinoma of the body of the pancreas may show no function or poor function even in the absence of jaundice and gallstones.

The fluid obtained by duodenal drainage will usually contain little or no bile in carcinoma of the head of the pancreas but may contain gross blood. Examination of a twenty-four hour collection of stool usually discloses rather low values for stercobilin.

Diagnosis:—The diagnosis of carcinoma of the pancreas is usually not difficult. Lesions of the head of the pancreas must be differentiated from nonmalignant causes of jaundice such as cirrhosis, hepatitis in its various forms, carcinoma of the ampulla of Vater and stones in the common bile duct. The diagnosis is easy when one is confronted with a patient who presents a history of rapidly progressive weakness, anorexia, loss of weight and strength, painless jaundice and a palpably distended gallbladder, along with absence of bile on duodenal drainage. It may not be quite so easy when there is a history of disease of short duration, when the symptoms are minimal and when the gallbladder is not palpable. In such cases the negative results obtained with the various tests of hepatic function, particularly the flocculation tests, the normal albumin/globulin ratio and the failure to find bile in the duodenum on repeated duodenal drainage (making sure the tube is in the duodenum) aid considerably in the diagnosis.

Whenever the jaundiced patient who has been losing weight and strength is found on roentgenoscopic study to have a widened duodenal loop or to have a supernormal concentration of amylase and lipase in the blood serum, the possibility of pancreatic malignancy can be strongly suspected.

A diagnosis of carcinoma of the body of the pancreas often has to be made almost exclusively on the basis of the history and clinical features since all the laboratory studies may give negative results. The diagnosis is often most difficult during the early part of the disease. Perhaps this accounts for the common finding of extensive metastasis at exploration. The acquisition of lumbar backache, even though mild but persistent from day to day, should arouse suspicion, particularly if it interferes with sleep. The presence of a bandlike distress across the abdomen and upper lumbar region of the back which is worse in recumbency and partly relieved by sitting up, along with loss of weight, strength and appetite and perhaps some acquired constipation, is very suggestive of malignancy of the body of the pancreas. The patient will often be found sitting on the edge of the bed or in a chair leaning forward. Not uncommonly he may sleep part of the night sitting up in a chair. Even when pain eventually becomes constant day and night there may be a dearth of physical and laboratory findings. Sometimes retention of sulfobromophthalein and enlargement of the liver may be the only positive findings in carcinoma of the body of the pancreas.

A duodenal or gastric ulcer perforating onto the pancreas may produce similar pain but such pain from ulcer is usually not constant, there is generally a

history of earlier distress from ulcer, and great loss of weight and strength usually has not occurred. A retroperitoneal sarcoma can simulate a malignant tumor of the pancreas.

Since the only treatment that offers any hope is surgical removal before metastasis has occurred, it is the obligation of the clinciian to try to make the diagnosis much earlier than has been the custom to date.

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SURGICAL ASPECTS OF PANCREATIC DISEASE*

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Surgical therapy has been utilized in pancreatic disease for many years but until recently the results have been discouraging. The anatomical situation of the pancreas has caused considerable technical difficulty and the physiological disturbances created by operation have been poorly understood.

With advances in technic and the use of antibiotics and improved anesthesia, the mortality has been considerably reduced. Operations on the pancreas have become relatively common, and it is now possible to evaluate the results of pancreatic surgery. A variety of lesions are amenable to surgical therapy.

I. *Congenital Anomalies*
   a. Aberrant pancreas
   b. Annular pancreas

II. *Inflammatory Lesions*
   a. Acute pancreatitis
   b. Chronic relapsing pancreatitis and pancreatic lithiasis

III. *Tumors*
   a. Islet cell adenoma
   b. Cystic tumors and pseudocysts
   c. Carcinoma of the head and ampulla of Vater
   d. Carcinoma of the body and tail

IV. *Traumatic Lesions*
   a. Pseudocysts
   b. Fistula

Congenital Anomalies

Aberrant pancreas:—Aberrant pancreatic rests may occur anywhere within the peritoneal cavity. In published reports, the duodenum is the most common location; stomach and small bowel are next in frequency, while the gallbladder, mesentery and omentum are rarer sites. Clinical symptoms occur in about half the cases, the type depending on the location of the heterotopic rest. In the stomach, these lesions may produce ulcer symptoms and pyloric obstruction; in the bowel, intussuception; in other areas they may be the source of bleeding or become the site of acute pancreatitis. The treatment is surgical resection of

*Read before the Sixteenth Annual Convention of the National Gastroenterological Association, Chicago, Ill., 17, 18, 19 September 1951.

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the pancreatic rest, not only for the relief of symptoms but also because of the danger of malignant change[1].

Annular Pancreas:—This rare anomaly has aroused considerable interest and a great deal of discussion has centered about its proper surgical treatment. The pancreas develops from a dorsal and a ventral anlage. Normally, the dorsal anlage forms most of the organ and the vetnral contributes to the formation of the head. In rare instances, due to overgrowth of the ventral anlage or to abnormalities in rotation of the duodenum a ring of pancreatic tissue surrounds the second part of the duodenum. Cattell and Warren[2] state that ⅓ of the patients with this anomaly have symptoms and these may be due to duodenal obstruction by the encircling band, to an associated duodenal atresia or to peptic ulcer which exists as a complication.

The treatment is surgical and it has become increasingly evident that division of the constricting band is not the treatment of choice. This procedure often

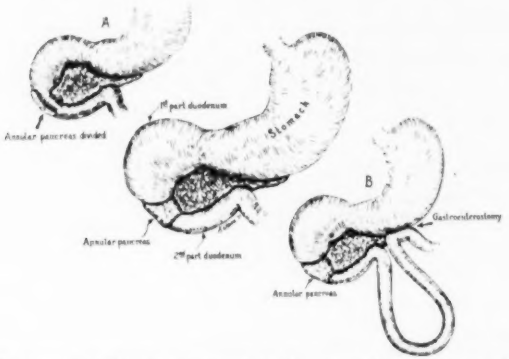


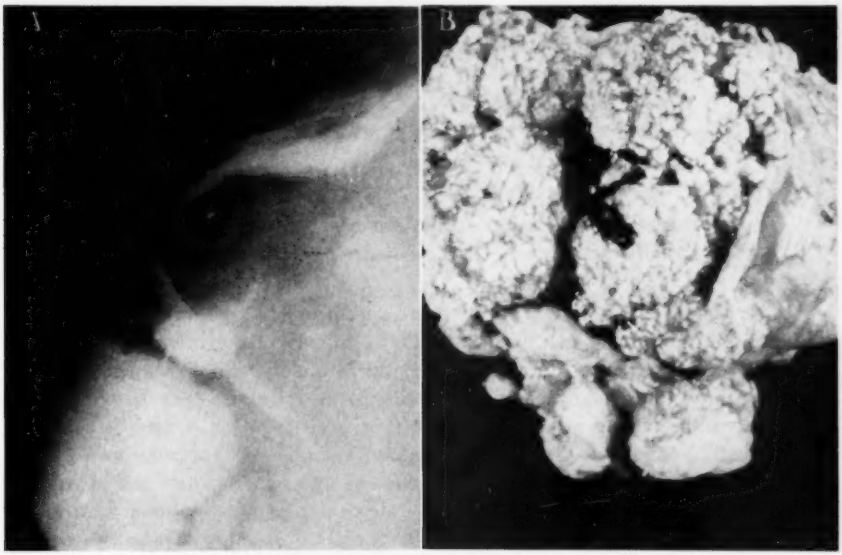
Fig. 1—Annular Pancreas. Methods employed in the surgical treatment of this anomaly.

fails to relieve the symptoms and is likely to be complicated by a postoperative pancreatic fistula. The obstruction should be short-circuited by a gastroenterostomy or by subtotal gastrectomy if a duodenal ulcer is present.

Inflammatory Lesions

Acute Pancreatitis:—Acute pancreatitis has been of surgical interest for many years. This condition must always be considered in the differential diagnosis of acute upper abdominal pain. In most clinics, if the diagnosis can be definitely established, the treatment is conservative and the only indications for surgery are the suspicion of a perforated viscus or the presence of an expanding intraabdominal mass. If the abdomen is explored and acute pancreatitis is found, the gallbladder is drained and the abdomen closed with as little manipulation as possible.

The conservative therapy of acute pancreatitis has improved tremendously in recent years. Lium and Maddock[3] have pointed out that in experimental pancreatitis the two important etiological factors are obstruction to the pancreatic duct and an active enzyme-rich pancreatic secretion. The acute hemorrhagic type of pancreatitis seldom if ever develops in a nonsecreting gland no matter what the cause of the ductal obstruction. Ripstein and Thompson[4] have demonstrated that bilateral vagotomy reduces the mortality of experimental pancreatitis in dogs by decreasing the enzyme output of the gland. Subsequent experience with banthine in the experimental animal and in clinical cases has proved it to be a most valuable aid in the therapy of this disease. We have noted recently that aureomycin further reduces the mortality of experimental pancreatitis and in the



a b

Fig. 2—a. Lateral x-ray demonstrating pancreatic cyst which is displacing the stomach anteriorly. This cyst has persisted despite drainage.
b. Papillary cystadenoma of the pancreas resected at operation.

past two years we have treated 20 cases of acute pancreatitis with two deaths, a mortality of 10 per cent compared to a previous figure of 35 per cent in 64 cases up to 1943. It has been interesting to note that since the more severe cases of acute pancreatitis are surviving the initial attack, the incidence of pseudocysts has increased.

Chronic Relapsing Pancreatitis:—Comfort, Gambill and Baggenstoss[5] have clarified the clinical picture of this entity and we now recognize that many cases of vague upper abdominal pain and dyspepsia fall into this category. The frequent asscociation of chronic pancreatitis with gallbladder disease has focussed

the surgeon's attention on the biliary tract but the results of such surgery have been disappointing. There is no doubt that cholecystectomy and choledochostomy should be tried but when these fail to control the disease, the surgeon faces a perplexing problem. Many procedures have been advocated but none is universally successful. They can best be grouped under the following headings:

1. *Attempts to overcome obstruction at the sphincter of Oddi*
   a. Dilatation of the sphincter
   b. Sphincterotomy
   c. Diversion of the biliary stream by choledochojejunostomy

2. *Attempts to diminish pancreatic secretion*
   a. Subtotal gastrectomy
   b. Vagotomy

3. *Sympathetic denervation of the pancreas*

4. *Direct attacks on the pancreas*
   a. Removal of pancreatic duct stones
   b. Pancreatectomy—partial or complete.

The operations designed to overcome spasm or obstruction at the sphincter of Oddi are based on the theory that biliary reflux into the pancreatic duct is the cause of recurrent pancreatitis. Doubilet and Mulholland[6] have shown that such reflux does occur in many cases of the disease in man and they have reported favorable results from sphincterotomy. Our own experience has been disappointing. The immediate results are sometimes good, but in a long term follow-up, most of these patients have had recurrent attacks. Bowers[7] has advocated complete diversion of the biliary flow by anastomosing the common duct to the duodenum or a "Y" loop of jejunum. This procedure would expose the patient to the theoretical danger of ascending cholangitis. It has, however, given good results in two personal cases and should be considered the operation of choice when a tight fibrous stricture of the sphincter is present.

Richman and Colp[8] feel that subtotal gastric resection is of benefit in this disease. This operation diverts the acid gastric contents from the duodenum and thus cuts down the stimulus to pancreatic secretion. We have employed vagotomy and gastroenterostomy to accomplish the same effect. The results in three patients have been disappointing. All have had further attacks since operation.

The idea of controlling the pain of pancreatic disease by sympathetic denervation is appealing. Many surgeons have reported excellent results with this procedure[9]. Here again, personal experience tempers enthusiasm. The initial

results of sympathectomy have been encouraging but in many cases they have been temporary and in a few years the patients have had recurrent symptoms.

Direct surgical attack on the diseased pancreas has become feasible in recent years. Cattell has been the chief advocate of this approach and there is no doubt that pancreatic resection does alleviate the pain of chronic pancreatitis. However, the mortality is still too high to justify such a procedure except in extreme cases where all other measures have failed.

At the moment, the surgeon has no really satisfactory treatment for this condition although the elimination of biliary tract pathology, diversion of bile

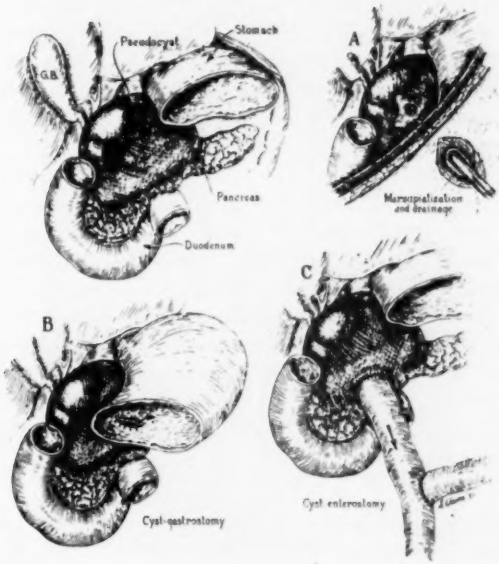


Fig. 3—Pseudocyst of the Pancreas. Surgical procedures employed in the treatment of this condition.

where an organic stricture of the sphincter of Oddi exists and the judicious use of sympathectomy or distal pancreatic resection may provide relief for many of these patients.

Tumors

Islet cell adenoma associated with hyperinsulinism has become a well-defined clinical entity which usually responds to surgical therapy. As the differential diagnosis of hypoglycemia has become more exact, the number of negative explorations has decreased. However, the surgeon must recognize that

the tumor may be small, it may be located in the head of the pancreas as well as in the body or tail and in 10 per cent of cases, multiple tumors exist. If no adenoma can be found, distal pancreatic resection should be carried out. The results of this procedure are satisfactory in half the cases, in the remainder symptoms recur and occasionally total pancreatectomy is necessary to obtain relief.

Cystic Tumors of the pancreas must be differentiated from pseudocysts because the treatment is entirely different. A biopsy of the cyst wall will usually settle the question by demonstrating epithelium in the case of the true cyst.

In dealing with cystadenoma, the principle of marsupialization has been overdone and these tumors should be treated by excision. Malignant degeneration has been frequently observed, and although the risk of excision is undoubtedly great the end results are far superior to drainage. Figure 2 shows a cyst which persisted despite drainage. At re-operation, a papillary cystadenoma was excised and the patient made an uneventful recovery.

The pseudocyst presents a different problem. These lesions usually follow trauma or acute pancreatitis and they are not tumors but encapsulated collections of fluid in the lesser peritoneal sac which produce symptoms by pressure on adjacent organs. Excision is seldom possible because the cyst has a broad base and there is usually a great deal of inflammatory reaction in the surrounding tissues. Drainage of the cyst is the operation of choice. Internal drainage by anastomosis of the cyst of the stomach or jejunum has been recommended but in our experience has met with frequent failure. We have found that the gastrointestinal contents tend to collect in the cyst and other dangerous complications such as hemorrhage may ensue.

External drainage of the pseudocyst is simple and safe and although a pancreatic fistula does result, most of these will close in time. Many of the bad results of simple drainage are due to the misuse of this procedure in cystadenomata (Fig. 3).

Carcinoma of the Pancreas:—Carcinoma of the head of the pancreas and of the ampulla of Vater can be considered together because they give rise to similar clinical manifestations and require similar treatment.

Because of their location these tumors cause obstruction to the bile and pancreatic ducts. This results in jaundice and a decrease in the pancreatic enzyme content of the duodenal aspiration[10]. The presence of these findings makes exploratory laparotomy mandatory. At operation, considerable difficulty may arise in differentiating carcinoma from chronic pancreatitis but with increasing

experience and the use of pancreatic biopsy it is usually possible to make diagnosis.

If the lesion is not fixed and if no metastases are present, the treatment of choice is radical pancreaticoduodenectomy. In a previous presentation before this Association[10], it was pointed out that the radical operation can be performed with an acceptible mortality and that the gastrointestinal tract can be reconstituted so that it functions in a satisfactory manner. It was also pointed out that the weak point in the operation is the necessity of preserving the superior mesenteric vein and a method was suggested to obviate this difficulty.

Fig. 4—Early carcinoma of the pancreas surrounds a dilated duct. This patient is alive and well four years after radical resection.

Despite these advances, the results of radical resection in carcinoma of the head of the pancreas remain poor and few 5 year survivals have been reported. The longest survival in our series has been 4 years with the patient still alive and well (Fig. 4). However, the radical approach offers the only opportunity for cure and as long as occasional successful results are reported, the operation is justified.

Carcinoma of the ampulla offers a much better prognosis. These tumors remain localized and do not metastasize early. Many long term survivals are reported following radical resection and even where the tumor is large, it is

often confined to a local area so that exploration is always indicated. Carcinoma of the body of the pancreas presents an even more gloomy picture. The technical procedure of resecting the body is not difficult, but almost invariably, by the time the diagnosis is made and laparotomy performed the growth has spread. I have yet to encounter an operable case of carcinoma of the body of the pancreas and the results reported in literature are almost equally disappointing. It appears likely, however, that with earlier diagnosis some of these tumors may be resectable and curable.

Summary

1. The present status of surgery in pancreatic disease has been reviewed.

2. The mortality of pancreatic surgery has decreased so that more lesions are now amenable to operative procedures.

3. The results of pancreatic surgery are improving as experience accumulates.

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Discussion

Dr. M. I. Grossman (Chicago, Ill.):—I should like to commend the essayists on presenting this broad subject in such a comprehensive and understandable fashion. There are just a few points which I should like to raise, of particular interest to me as a physiologist.

First, I should like to comment on the large factor of safety which is present in the pancreas, so that the symptoms of deficiency of digestion which arise when there is a total absence of pancreatic secretion from the intestine, are not seen until very late in pancreatic disease. In the animal we can remove as much as 80 to 90 per cent of its pancreas without producing deficiency of digestion. Similarly, in the human with pancreatic disease, it is not until the late stages of the disease, when a very large portion of the pancreas has been lost, that we find deficiency symptoms, and for that reason the symptoms of pancreatic disease are not those of digestive deficiency but those of a kind of perverted digestion, where the digestive juice of the pancreas attacks the pancreas itself or the surrounding tissues.

Secondly, I should like to say a few words about blood enzymes in pancreatic disease. It has often been felt that the occurrence of pancreatic enzymes in the blood is a pathological process; however, it has been known for some time and is currently being reëmphasized that at all times digestive enzymes enter the blood stream to some extent including those of the pancreas and of other digestive organs. This is a kind of endocrine secretion of a normally exocrine product. There is a certain small partition of enzymes into the blood stream under normal circumstances.

Under pathological conditions we find a marked increase in these enzymes. The one factor that has been widely recognized as contributing to this rise in serum enzymes is the rise in intraductal pressure produced by obstruction of the duct combined with stimulation of secretion. In this regard it can be shown that pressures within the physiological range, pressures that do not exceed those which can occur as a result of the secretory pressure of the pancreas, combined with the obstructive pressure of the spasm of the musculature of the duct and of the intramural portion of the duodenum, can give rise to an elevation of serum enzymes which is not accompanied by any pathological microscopical change in the pancreas.

The question arises as to whether rise in intraductal pressure is the only important contributory factor to rise in serum enzymes. I believe it is likely that the disruption of the pancreatic cells themselves may directly contribute pancreatic enzymes to the blood stream.

Next I should like to comment on ethionine-induced pancreatitis which Dr. Popper mentioned and first described in work from his laboratory. I believe that this ushers in a new era in our thinking about pancreatic disease because here, for the first time, we have an example of a metabolic disturbance in pancreatic function as contrasted with the mechanical ideas of obstruction, secretory pressure, regurgitation, etc. Since, as Dr. Popper has pointed out, there are so many deficiencies in these mechanical ideas, we are badly in need of new concepts which are able to account for the pathogenesis of pancreatic disease.

In our laboratory in the past year Dr. Ary Almeida has studied the ethionine-produced pancreatitis in dogs. He has confirmed the production of pancreatitis in this species and has done simultaneous functional studies on secretion of pancreatic juice from these animals whose pancreas has been damaged by the administration of ethionine. We have seen the whole series of changes which Dr. Popper described in the rat, also occurring in the dog, going from minor inflammatory and edematous changes on through vacuolization, necrosis, and fibrosis.

The functional changes which accompanied these microscopic changes were not of severe grade until a very severe picture microscopically was present; in

other words, with moderate grades of histological damage, the ability of the pancreas to secrete was relatively unimpaired.

I should like to comment briefly on the surgical principles in the management of pancreatic disease which Dr. Ripstein covered so well and so judiciously. There are two points that I should like to raise: first, that it is well-known physiologically that acid is not the sole stimulus for pancreatic secretion, although it is historically the one which has been most widely studied and publicized. It is well-known that fat and protein are strong stimuli for pancreatic secretion, therefore control of acid alone may not be adequate for regulation or reduction of pancreatic secretion in pancreatic disease. Secondly, I should like to point out that current evidence indicates that the hormonal control of pancreatic secretion by pancreozymin and secretin is probably of predominant importance in the normal stimulation of pancreatic secretion and therefore operations which are directed only toward the neural control can be expected to be deficient in reducing satisfactorily pancreatic secretion.

Finally, I should like to make a comment and address a question to Dr. Gambill. It seemed to me from Dr. Gambill's very fine presentation that in regard to the secretin test, he damned it by faint praise. Now Dr. Gambill and Dr. Comfort and their group at the Mayo Clinic have had very extensive experience with the secretin test, and from my reading of their papers, I have been impressed with the utility of the secretin test in uncovering pancreatic disease in that large group of patients that lies between those with the acute attack having a rise in serum enzymes, and those with late sequelae such as steatorrhea, diabetes, and calcification. This intermediate group constitutes a considerable group of patients, and the secretin test appears in those instances to be the only positive diagnostic test for the establishment of pancreatic disease.

I should like to ask Dr. Gambill if he doesn't feel that the secretin test is valuable for uncovering these early cases of pancreatic disease, particularly at the time when they may be susceptible to successful medical management.

Dr. Anthony Bassler (New York, N. Y.):—I want to express my personal thanks and appreciation to the gentlemen who have entered into this discussion on pancreatic disease which I think is the best that I have ever heard. It is a subject that still requires a great deal of study, as you must know. The conclusions you see are so indefinite—everything is so difficult about it, but as we go on year after year, we accumulate a little more knowledge.

I have never seen the rationale of the secretin test. A pancreas will accumulate those substances which make for amylase particularly. The secretin test immediately purges the pancreas. That is probably the reason why the amylase

increases in the blood in the early hours of acute pancreatitis. It is simply an inflammatory stimulation effect causing a sudden discharge.

One gets much better clinical values without the secretin test, using the ordinary stimuli of fat or 5 per cent protein solutions. In a carcinoma of the pancreas or when there is any definite condition like that, one gets no results in the way of enzymes from the pancreas. That is almost classical and is an important diagnostic point, but when you deal with chronic pancreatitis, you have enzyme values, and with secretin the values are erroneous.

I am a little interested in the incidence of alcoholism as the cause of chronic pancreatitis. In the twenty cases that we had, we had one denial of drinking alcohol, and that woman is not to be considered in my opinion, because I take her veracity as not to be depended upon. Alcohol is undoubtedly a factor, and therefore its importance cannot be eliminated in a therapeutic way.

In one of the hospitals I belong to, one of the boys said to me one day, "Whenever I do a histamine test and the gallbladder has been removed and the patient did not get any better, I suspect we are dealing with an instance of chronic pancreatitis." That is an interesting thing because in every case of chronic pancreatitis that one sees (except in the fibrocystic cases) the gallbladder has been removed—and one of the interesting things about it is that there was not much wrong with the gallbladder. There is a pathological report about the same as seen with an appendix after forty years of age. It is pathologic but there are no adhesions and nothing much to be talked about, but what is interesting and what often does not go down on the operative records in the hospitals and seems to be lost, is the incidence of fatty liver. I think if you operate for the possibility of gallbladder disease and you meet with a fatty liver, you should suspect chronic pancreatitis right away.

Mention has been made of the dosage of pancreatin. I think the doctor mentioned 15 grams a day. My experience is that one gets very little benefit from that. That is much too small a dose. You have got to give tablespoonful doses after meals to get any benefit at all, and that benefit never comes in relief of pain. It does come by increasing and stimulating a better nutrition on the part of the patient. These cases of chronic pancreatitis are all very much reduced people, and to gain a pound or two is quite a job for them. The best preparation of pancreas I have used so far is viokase.

Our experience has also been that most of these cases require help for relief of pain in a more or less continued way, especially in the calcareous cases. We have not done very well with demerol, but have done very much better with dolophine or dromoran.

Again I want to express my appreciation to the essayists.

Dr. Hans Popper (Chicago, Ill.):—I am very thankful to Dr. Grossman for giving support to the idea that protein deficiency or metabolic changes may start at least some of the inflammatory lesions of the pancreas. The excellent presentations of Dr. Gambill and Ripstein have not only also emphasized the importance of chronic relapsing pancreatitis but have also made it clear that the pathogenesis of the lesion is still not fully established. Again, I would like to present a plea to consider the possibility that the first step in the vicious cycle characteristic of this disease may be a metabolic deficiency and that the relation between liver and pancreas be here seriously considered. The pancreas has been thought of as the guardian of the liver. Dr. Bassler has referred to this relation between pancreas and liver; it seems to be rather complicated and many aspects are today not fully understood, for instance, why in acute pancreatic necrosis so often, apparently rapidly, a fatty liver develops.

At the autopsy table pancreatitis may be the solution to a most bizarre and unexpected course of events. I want to mention two examples: one is a patient on whom a gastroenterostomy was performed because of a questionable, never fully established duodenal ulcer. Repeated attacks of gastrointestinal hemorrhage ensued from subsequently developing marginal and jejunal ulcers. The basic lesion was a relapsing pancreatitis not detected at operation, but facilitating the development of the marginal ulcers because of faulty neutralization of the acid secretion. The second example represents a woman who was admitted to the hospital in renal failure, to which she succumbed. Repeated attacks of diarrhea during the last 6 months were interpreted as dysentery. The basic lesion was again a chronic pancreatitis which caused as well the diarrhea as an unrecognized diabetes which in turn produced a fatal papillary necrosis of the kidney. To me, chronic pancreatitis still remains the big diagnostic and therapeutic problem in the diseases of the pancreas.

Dr. Earl E. Gambill (Rochester, Minn.):—I, too, want to express my appreciation for the fine discussions which have been given. I have been very much stimulated and intrigued by the investigations which were reported by Dr. Popper and by Dr. Grossman that appear to be real advances in the study of pancreatitis. We need to think more of such possibilities and to broaden our concepts as to the possible causes of pancreatitis.

Sometimes I wonder if we may overdo the idea of the necessity of the common channel in the genesis of pancreatitis. I do not know of a good reason why regurgitation of bile and duodenal content cannot occur from the duodenum directly into one of the pancreatic ducts under certain abnormal conditions in the absence of a common channel. That is an idea that has come to me on numerous occasions.

With reference to the question regarding the dose of pancreatin, I believe that Dr. Bassler perhaps misunderstood me. The dosage mentioned was 2 to 10 grams three times daily which would total 6 to 30 grams. I heartily agree with him that the small dose of only 2 to 10 grams per day would not be sufficient in the control of pancreatic steatorrhea.

Dr. Grossman has brought up the point about the secretin test. I hope I did not give the wrong impression, for I do not wish to belittle the test. I think that it has value. We have used it occasionally. From the practical standpoint, however, I don't think it is often necessary to perform this test to make a diagnosis of pancreatitis when one is seeing a patient who has recurrent attacks of pain. In most instances, the diagnosis can be made without the test. There is a practical aspect to the use of this test. If one sees a patient who has an attack of pain, in the early stages of the disease, an accurate history and the determination of the concentration of serum amylase and lipase during such an attack seems to be a simpler way of establishing the diagnosis of pancreatitis. Moreover, it is obviously not very practical to try to put a tube down into the duodenum to do a secretin test during one of the episodes of pain. I have not used the secretin test very much but it seems that it is more reliable later in the disease when there has been so much destruction of the pancreas that the pancreatic enzymes in the blood are no longer elevated during the attacks of pain. By this time, however, often such complications as steatorrhea or pancreatic calcification may have appeared, and help confirm the diagnosis in an indirect manner. The secretin test has been of value in the diagnosis of chronic pancreatitis among those individuals who have had previous episodes of pain suggestive of relapsing pancreatitis, but who do not present evidence of unquestionable steatorrhea, and who are studied at a time when they are not having an acute episode of pain.

Dr. Charles B. Ripstein (Brooklyn, N. Y.):—I, too, would like to thank the discussers for their very kind remarks. On the point that Dr. Popper has brought up, I think that we surgeons are definitely at fault. I am sure a great many people have laparotomies for upper abdominal pain, cholecystectomies or operations for duodenal ulcer, when the basic condition is a chronic pancreatitis, which is not recognized at operation. It is not easy to recognize the presence of pancreatic disease if you are not looking for it, and I have personally seen a surgeon run a hand over the place where the pancreas should be and say it is indurated, or it feels normal, and unless it is so grossly involved that it hits him in the face, he doesn't suspect the presence of disease.

I think it is the responsibility of the gastroenterologist, as well as of the surgeon, to insist that the pancreas be thoroughly explored in these cases, and perhaps biopsied. I don't have any great fear of biopsy of the pancreas. Very seldom do we see harmful results, and the establishment of a definite diagnosis

of chronic pancreatitis, rather than the removal of the gallbladder or performance of a gastrectomy, may give a great deal of help in further care of the patient.

CANCER CHEMOTHERAPY*

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A serious investigative effort is now under way, at the Memorial Center and elsewhere, to achieve the chemical control of disseminated neoplastic disease. Although the results to date cannot be classed as clinical cures, the data are felt to be significant enough to merit some interest on the part of the clinician.

The effort presently under way is based upon a concept somewhat at variance with the thesis ordinarily held regarding cancer. We hold the opinion that for too long the neoplastic process has been shrouded in an aura of mystery. It has been viewed as a problem that can be solved only by the providential

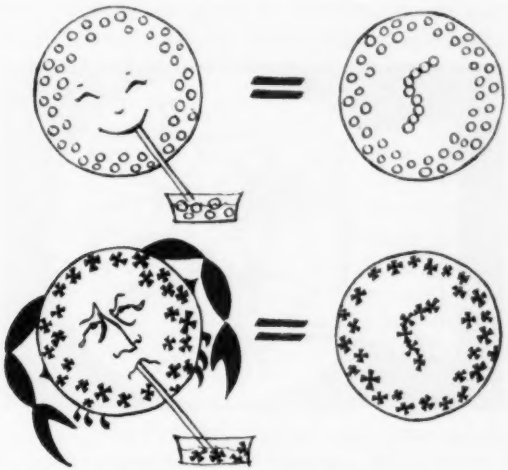


Fig. 1—The characteristics of the cell are determined by the components of its chromosome, which are repaired or replaced according to the needs of the particular type of cell. If the cancer cell can be shown to have different nutritional requirements from the normal cell, its preferred food might be poisoned.

disclosure of some secret of nature as yet unknown. As a consequence, almost every type of investigative effort in a biological field has been imagined to apply to the clinical control of cancer in man, on the grounds that only by such random exploration will a cure be found.

Careful survey of the subject reveals that perhaps it is not necessary to be so pessimistic. On the contrary, it seems not impossible that the neoplastic

*Read before the Sixteenth Annual Convention of the National Gastroenterological Association, Chicago, Ill., 17, 18, 19 September 1951.

process may be regarded simply as another type of invasion by a cell—a cell autogenous in origin in contradistinction to the ordinary exogenous invader—and so can be attacked precisely as one would attack parasitic or infectious invaders.

Intensive work along this line has given us much evidence in support of the view presented. It is now possible to induce growth of metastases from human or animal neoplastic cells inoculated into several animal species, provided the potential hosts are of the proper age (usually weanlings) and that their natural defense is somewhat reduced by irradiation (Toolan). A variety of human neoplastic cells have been transplanted. These behave in the experimental animals very much as experimentally induced invasive infection.

Secondly, from the work of Burchenal, confirmed by Law, it has been clearly shown that the neoplastic cell, properly handled, will evince all the phenomena of adaptation to therapeutic agents which are shown by infectious

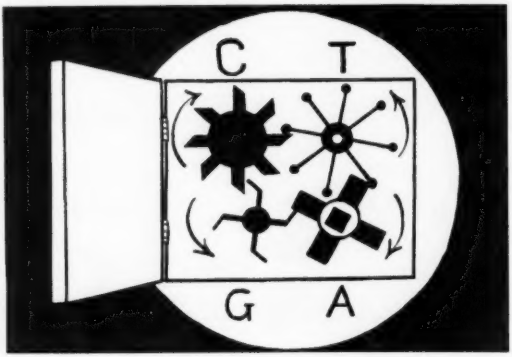


Fig. 2—The four principal components of the nucleic acid of the chromosome interact with each other, something like the gears in a switchboard, to control the chromosome's processes.

invaders. One can breed a race of chemically resistant cancer cells, human or animal, exactly as one can breed a race of streptomycin-resistant tubercle bacilli or other types of refractory microorganisms.

We regard these two pieces of evidence as of considerable importance. The problem of cancer chemotherapy as a whole, for the purpose of this discussion, can be divided into two basic parts. The first, which need only be mentioned briefly here, has to do with the treatment of cancer which is still semi-dependent. Familiar examples are: the patient with prostatic cancer which can be controlled by feminization; the patient with mammary cancer controlled similarly by altering the endocrine balance. It is quite clear that these forms of cancer are somewhat dependent on their environment, and in this respect resemble their nor-

mal, parent cells. When, by mutation, they lose the characteristics which make them controllable by such a therapeutic regimen, however, they are no longer dependent but can be regarded as autonomous microorganisms, differing radically from the host cells which gave them rise and which they invade.

For almost the first time in medical history, there has been instituted a substantial investigative effort based upon this simple theme. At the risk of, perhaps, oversimplifying, I have taken the liberty of illustrating my points with symbolic drawings. The program is too complex and too extensive to present in all its biochemical detail at this time.

Clinicians are, of course, concerned with the potential practical application. It should be emphasized at the beginning, then, that there is today no curative chemical agent for cancer in man. Such palliative value as can be observed is only in exceedingly sensitive and rapidly growing forms of neoplastic disease—usually of the lymphatic tissues. There is no evidence, unfortunately, of control of cancer of the gastrointestinal tract.

The basic principle underlying this search for therapeutic agents is illustrated in Figure 1. The upper symbols represent a benign normal cell; the lower ones, a neoplastic cell, marked with the crab, the classic symbol for cancer. If one wishes to destroy one class of cells, in this case the neoplastic, and leave others, the normal cells, unharmed, one must decide upon a procedure. At the Sloan-Kettering Institute, an effort is under way to analyze the peculiar nutritional needs of the two types of cells. Thus if the one we wish to destroy were found to have peculiar specific appetites, its preferred food could be rendered poisonous or radioactive, and it might thus be selectively destroyed.

In order to establish differential chemical needs of two different types of cells, one must decide what particular component of the cells to analyze, and what means to use for analyzing this component. In the case of our study of normal as compared with neoplastic cells, it was thought reasonable to develop means for analyzing the comparative anabolic processes of the chromosome.

This cellular component was selected for study because all of the characteristics of different cells are dependent, apparently, upon the chromosome and its genes. There is ample evidence to justify this supposition. The work of Beadle, confirmed by a variety of laboratories, has indicated that for each enzyme operative in the cell's metabolic processes, there is one gene. This so-called one-gene-one-enzyme hypothesis is now well established.

It was hoped that the chromosome, like other cellular constituents, is in dynamic equilibrium; its parts constantly wearing out and being repaired by new ones instead of remaining static. In order to deprive the cancer cell of its

essential enzymatic constituents, while leaving the normal cells undisturbed, it seemed reasonable therefore to look for a difference in the mechanism which controls these constituents and their building up and breaking down processes in the two types of cells. If one could show that the normal cell repaired its chromosome with different materials, or different amounts of some of these materials, than does the cancer cell, one would have a lead to cancer chemotherapy.

An analytical procedure by which we can define a difference in the chemical needs of the chromosomes of normal and neoplastic cells has been under development. It has revealed, as very simply expressed in Figure 2, the fact that the nucleic acid which is the principal component of the chromosome is, in turn, composed of four principal chemicals: two purines and two pyrimidines. These are indicated by the letters C, T, G, and A. These four characteristic chemicals interact with each other, like the gears in a control board, to govern the chromo-

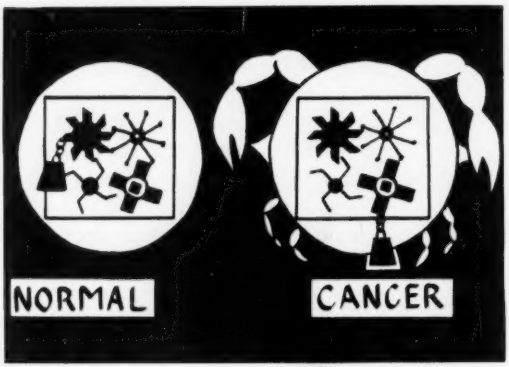


Fig. 3—An atomic marker, or weight, attached to materials which might be used by the chromosome in its repair, indicates which materials are taken up and in what quantities.

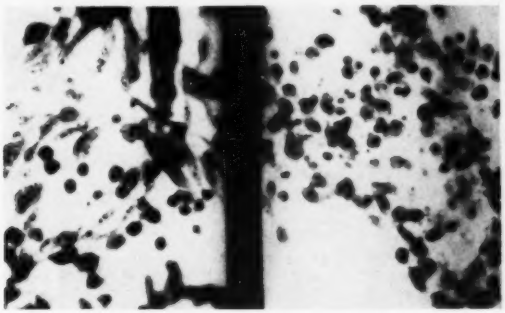
some's processes, the functions of the cell which they serve, and the daughter cells to which they give rise.

It now has been shown that these chemicals are not static in the nucleic acid of the chromosomal structure, but rather they are being constantly worn out, replaced and repaired by the incorporation of new chemicals of this type. This is a very important finding indeed. Only the development of new methods permits its further definition.

We have, furthermore, good evidence that different types of cells require different amounts of these peculiar chemicals. For example, as shown diagrammatically in Figure 3, by the use of radioactive or heavy tracers it is hoped to demonstrate that one chemical is replaced very much more frequently in the nucleic acid of the cancer cell than is the case in the concomitant normal cell.

In the normal cell perhaps there is more frequent replacement of one component, but of a different one than in the cancer cell. This, again, is a generalization subject to considerable modification, but good evidence supports the principle that there is a curious specificity of the chromosomal nucleic acid anabolic process, which varies from cell to cell and differs between cancer cells and normal cells.

Once this was known, it became necessary to obtain a vast number of compounds analogous to the purines and pyrimidines used in the building up of different types of chromosome material in the body. By arrangement with cooperating university and pharmaceutical laboratories, suitable modifications of these potential repair parts of chromosomes were provided, with particular reference to the sort especially needed by cancer cells. These compounds then were so modified as to be possibly poisonous or abnormal enough to impair the function of the cancer cell.



a b

Fig. 4—a. Sarcoma T241 cells of untreated culture.*
b. Sarcoma T241 cells of culture treated with 0.4 mM of diaminopurine hydrochloride per liter.*

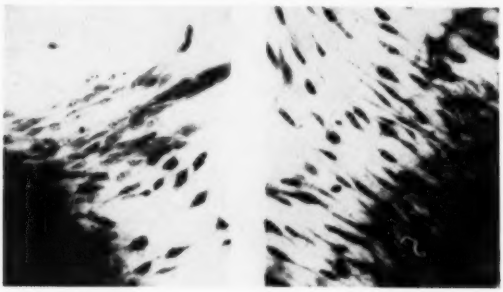
In order to prove that a particular chemical would exert a selective injury to the neoplastic as compared to the normal cell, it was necessary to find sufficiently delicate assay methods. A very sensitive test was developed by Dr. Biesele. Following his technic, normal and neoplastic cells are grown side by side in the same culture, both growing at the same rate, as judged by mitotic counts. The chemical to be tested is added to this cutlure and the comparative injury to the two types of cells is observed.

By this method it has been demonstrated that when cancer and normal cells are exposed equally to certain abnormal precursors of nucleic acid, cancer cells of certain types are specifically injured. Figure 4 shows the mouse sarcoma T-241 and normal mouse embryo skin, untreated and after exposure to equal

concentrations of 2,6-diaminopurine. The cancer cells, after treatment, have curled up and died. The normal cells suffered no such deleterious effect.

The establishment of this principle of selective injury of cancer cells as compared to normal cells seems to me of the utmost importance. For over a century everyone had said that it was impossible, just as everyone said that the killing of bacteria was impossible until it was accomplished. At the present time there are compounds which have demonstrated a thousand times as much toxicity, under the circumstances described, for cancer as for normal cells.

Such selectively injurious effects, of which there are many examples, are not limited to *in vitro* experiments. Recently for the first time, in our experience at least, it has become possible regularly to cure certain types of actively growing



c d

Fig. 4—c. Embryo mouse-skin cells in untreated culture.
d. Embryo mouse-skin cells in culture treated with 0.4 mM of diaminopurine hydrochloride per liter.*

Studies on 2,6-diaminopurine and related substances in cultures of embryonic and sarcomatous rodent tissues. John J. Biesele, Ruth E. Berger, Anne Yates Wilson, George H. Hitchings and Gertrude B. Elion, Cancer,* **4:186, 1951.

transplantable tumors in experimental animals. A great many compounds have been developed under this experimental chemotherapy program which exercise restraint on cancer growth, but only in this last year have we found regular cure possible. Figure 5 shows two rats into which cancer tissue was implanted 20 days previously. The rat on the right received one of the folic acid antagonists for five days, starting one week after transplantation. The cancer is completely destroyed and will not grow again.

Six substances have now brought about cures of one or more tumors in our spectrum of 22 transplantable rat and mouse tumors. Most of these agents are perfectly familiar ones. They include two of the folic acid antagonists, two nitrogen mustard analogues, triethylene melamine or TEM, a compound now in extensive use for treatment of Hodgkin's disease, and one very crude antibiotic.

With several combinations of sensitive tumors and suitable agents the incidence of cure has ranged from 90 to 100 per cent. Spontaneous regressions of these tumors have not been observed except in rare instances.

For those who are theoretical rather than practical, this is a matter of little moment. I confess, however, that I find it heartwarming to be able to say that, with the proper tumor and the proper compound, one can, in the animal, achieve cures not possible hitherto.

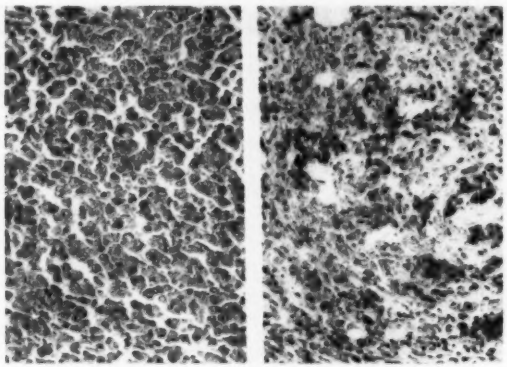
Fig. 5—The rapid growth of the sarcoma R39 in a control rat is contrasted with the much retarded growth of tumor in an aminopterin-treated animal (daily doses of 0.25 mg. per Kg. of aminopterin on five consecutive days). The tumors were photographed twenty days after implantation.*

**The effects of aminopterin on the growth of carcinoma, sarcoma and melanoma in animals. Kanenmatsu Sugiura, Alice E. Moore, and C. Chester Stock, Cancer, 2:491, 1949.*

Another way of selectively destroying the cancer cell is to use a living agent. There has been instituted recently an effort to train certain viruses to seek out cancer cells, to invade these cells and to destroy them. Now, through the conjoined work of our own laboratory and the Lederle Laboratories, no less than eight viruses have been shown to have the ability to destroy cancer cells in experimental animals. Most of these viruses are neurotropic and, in the mouse, as

they destroy the cancer they also infect the central nervous system so that the animal eventually dies.

It has been found that continuous passage of the viruses through tumor tissue greatly enhances their ability to destroy cancer cells. We now have a virus (RSSE) which will completely destroy one form of cancer, Sarcoma 180, in the mouse in 24 hours, as shown in Figure 6. The virus goes first to the tumor, multiplies most rapidly there, and destroys it completely. The affinity of the virus for normal tissue in the mouse has not been significantly decreased, however, and in the end the animal succumbs to the infection. If the survival period after destruction of the tumor can be sufficiently lengthened, it is hoped that a



a b

Fig. 6—a. Histological appearance of sarcoma 180. Hematoxylin and eosin stain.*
b. Histological appearance of sarcoma 180, showing the effects of virus infection on the tumor cells. Hematoxylin and eosin stain.*

The destructive effects of the virus of Russian Far East Encephalitis on the transplantable mouse sarcoma* 180. *Alice E. Moore, Cancer,* **2:525, 1949.

means can be found for controlling the virus and curing the animal of the subsequent infection.

It has been shown, furthermore, by experiments in mice, that a virus which will multiply in a tumor, but which does not ordinarily injure it, can be adapted to destroy the tumor if it is maintained constantly on the neoplastic tissue in question.

In other species, the training of the virus has been adequately achieved. As shown by the Lederle group, the use of trained Russian tickborne encephalitis virus will in every instance cure a form of cancer, leukosis, without injury to the fowl. This is the first example of a regular cure by a virus of cancer in the

experimental animal. Another example is provided by the work of Friedewald, who has trained a virus to destroy regularly rabbit fibroma without harm to the animal.

These data led logically to the effort by Dr. Southam and Dr. Moore to find viruses oncolytic in animals which would regularly infect human beings without causing any serious symptoms. A number of viruses fulfilling these criteria have been tried in patients with advanced cancer insusceptible to any form of treatment. For reasons unknown to us, not all patients are susceptible to each virus. With the West Nile virus, however, freshly isolated from man, many but not all the patients infected have developed viremia, but without neurological evidence of infection. This virus can be trained to destroy cancer in animals. Furthermore, it has been shown that after administration to patients with cancer this particular virus can, in some instances, be recovered from the tumor tissue after it has disappeared from normal tissue and the blood stream. In other words, the same principle obtains here as in the animal experiments: a virus will go to the human tumor tissue, multiply actively there, and remain there after it disappears from other tissues.

There has been, until recently, no method by which a virus could be trained to destroy human neoplasms. Now, within the last few months, procedures have been developed for growing human tumors in experimental animals. The technics for growing human tumors in tissue culture have been greatly improved. Thus we hope, as the years go on, to have a virus which will seek out cancer cells in man and destroy them.

This is simply a progress report. We have no therapeutic means at the present time beyond those with which all clinicians are familiar. It is of some interest, however, that our procedure of medical investigation has now reached a point at which there can be established an orderly program, based upon factual material, which can be reported upon as showing a certain amount of fundamental progress.

DIFFERENCES IN GASTRIC SECRETION IN NORMAL INDIVIDUALS AND PATIENTS WITH PEPTIC ULCER THEIR BEARING ON ULCER MANAGEMENT*

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The purposes of this paper are to review the data indicating that the gastric secretory response in patients with peptic ulcer differs significantly from normal and to demonstrate the importance of these differences in the management of peptic ulcer.

Nocturnal Gastric Secretion

The nocturnal gastric secretion measured for 12 hours by continuous aspiration of the stomach in normal individuals and patients with active duodenal ulcer and gastric ulcer differs significantly (Table I, Fig. 1). The average volume in patients with duodenal ulcer is approximately twice that of either the normal group or patients with gastric ulcer. In the majority of patients with duodenal ulcer the volume exceeded 800 c.c. whereas volumes were less than 800 c.c. in the majority of normal individuals and patients with benign gastric ulcer. There is no significant difference between normal individuals and patients with gastric ulcer.

The concentration of free hydrochloric acid in the total night secretion varies in the three groups. The average concentration in patients with duodenal ulcer was approximately twice that of normal individuals and three times that of patients with gastric ulcer. In the majority of patients with duodenal ulcer, the concentration exceeded 40 clinical units while in both the normal group and patients with gastric ulcer the values usually were less than 40. The lowest values were obtained in patients with gastric ulcer.

The differences between the three groups are more apparent when the output of free hydrochloric acid is computed. In normal individuals, the amount of free HCl secreted during the night averages 661 mg. The total output is less than 1,000 mg. in 84 per cent and below 500 mg. in 50 per cent of the latter, two-thirds were below 200 mg. In the gastric ulcer group, it was less than 1,000 mg.

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*Read before the Sixteenth Annual Convention of the National Gastroenterological Association, Chicago, Ill., 17, 18, 19 September 1951.

From Frank Billings Medical Clinic, Department of Medicine of University of Chicago.

in 85 per cent and below 500 mg. in two-thirds; the average output was 464 mg. On the other hand, the average output of free hydrochloric acid in patients with duodenal ulcer is 2,242 mg., a value more than three and a half times greater than that for either normal individuals or patients with benign gastric ulcer. The output in patients with duodenal ulcer exceeds 1,000 mg. in 81 per cent and 2,000 mg. in more than 50 per cent. An output less than 500 mg. was noted in only one instance*.

In a group of uncomplicated duodenal ulcer patients studied first at the time of active symptoms and when a crater was present, and again two months to three years after the ulcer had healed and during a period when they were free of ulcer symptoms, the following results were obtained[3]. The average nocturnal volume for the group during the active phase was 1,047 c.c., the free

TABLE I

THE AVERAGE 12-HOUR NOCTURNAL GASTRIC SECRETION IN NORMAL INDIVIDUALS AND IN PATIENTS WITH DUODENAL AND GASTRIC ULCERS

	Volume (c.c.)	Free Acid (Cl. units)	Total Output of HCl. (mg.)
Normal	581	29	661
Duodenal Ulcer	1004	61	2242
Gastric Ulcer	600	21	454

acidity 58 clinical units and the average output of free hydrochloric acid 1,957 mg. (Table II). In only one patient was there a significant decrease in concentration of free hydrochloric acid and in two a significant decrease in output of free hydrochloric acid after the ulcer had healed. On the other hand, a similar number of patients showed an increase in gastric secretion with healing of the ulcer. Thus, in the same patient with duodenal ulcer the twelve hour nocturnal gastric secretion is usually unaltered with healing of the ulcer; the nocturnal secretion in patients with healed duodenal ulcer is significantly greater than that of normal healthy individuals.

Additional studies on the nocturnal gastric secretion in a group of patients with intractable duodenal ulcer whose clinical course was characterized by severe pain and serious complications demonstrated an excessive secretion of acid in all cases, exceeding not only the mean for normal persons by four to ten

*For methods employed see References 1 and 2.

times, but surpassing also the general average for patients with duodenal ulcer[4]. These findings emphasize the important relationship of "intractable of hypersecretion" to "intractable duodenal ulcer".

Diurnal and Nocturnal Variations in Gastric Secretion

Quantitative measurements of the twenty-four hour gastric secretion and of the diurnal and nocturnal variations in gastric secretion in man heretofore have not been available. The *volume* of the twenty-four hour continuous fasting gas-

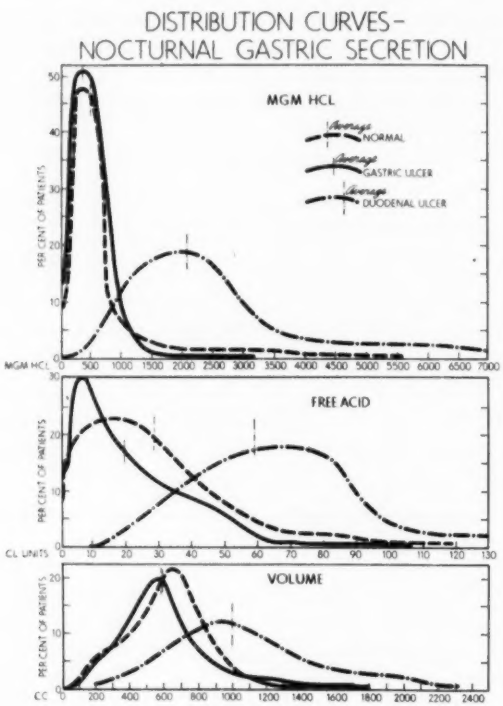

Fig. 1

tric secretion in the normal individuals varied from 518 to 1,568 ml., with an average of 1,072 (Table III). The range for duodenal ulcer was 1,141 to 2,064 ml., averaging 1,950. The average for gastric ulcer was 1,048, with a range from 352 to 2,211 ml. In eight of the ten normal individuals the volume was less than 1,500 ml.; in the remaining two cases of this group the volume exceeded 1,500 by 49 and 68 ml., respectively. In the duodenal ulcer group the twenty-four hour volume exceeded 1,500 ml. in all except three patients. In gastric ulcer the volume was less than 1,000 ml. in nineteen of the twenty-five patients.

The average *free acidity* for the normals was 49 clinical units, with a range of 0 to 72; as compared with an average of 57, and a range of 21 to 97 clinical units in patients with duodenal ulcer. The average concentration in gastric ulcer was 22 clinical units, with a range of 0 to 57.

The differences between the three groups again are most evident with respect to the output of free hydrochloric acid. The average for the duodenal ulcer series was 4,020 mg., as compared to 1,900 and 922 mg., respectively, for the normal and gastric ulcer groups. The twenty-four hour output of free hydrochloric acid exceeded 2,500 ml. in twelve of the fourteen patients with duodenal ulcer, three of the ten normal subjects and in only one pateint with gastric ulcer.

Comparison of Total Day Secretion with Total Night Secretion

The average total volume, concentration and output of free acid during the day and the night did not differ significantly in the normal group and patients with gastric ulcer. Individual evaluation of each case indicates that in the normal group the gastric secretion was higher during the day as frequently as during the night. On the other hand, in the gastric ulcer group, more patients secreted a larger volume during the day than during the night; however, the output of hydrochloric acid during the night and day periods did not differ significantly. The patients with duodenal ulcer differed from the other two groups in that usually the volume, concentration and output of acid during the night exceeded that produced during the day. For the entire group the average volume, concentration and output of acid in the night secretion exceeded the day scretion.

Hourly Values for Diurnal and Nocturnal Gastric Secretion

Gastric secretion was continuous in all three groups for the entire twenty-four hour period; absence of gastric content for one hour was very uncommon and in no instance was there an absence of secretion for as long as two hours. The average hourly secretion was significantly greater in patients with duodenal ulcer. There was no important difference between the hourly secretion of the normal group and of patients with gastric ulcer (Fig. 2).

In all subjects the rate of secretion varied from hour to hour in the same individual. Among duodenal ulcer patients, in contrast to the other subjects, a constantly higher secretory rate frequently was maintained for the entire twenty-four hour period. Under fasting conditons the average hourly secretion tended to be low during the morning hours (5:30 to 11:30 a.m.) in all three groups. After 11:30 a.m. the average hourly volume increased; the largest amounts were secreted between 5:30 and 11:30 p.m. After 11:30 p.m., the secretion again decreased. Thus, the rate of gastric secretion followed a definite diurnal and nocturnal pattern. In each instance the secretory rate in patients with duodenal

ulcer remained at a characteristically higher level throughout the twenty-four hour period.

The secretion of acid in patients with duodenal ulcer, in contrast to the other groups, was continuous under fasting conditions. Periods of anacidity lasting for only one hour were extremely rare in duodenal ulcer, whereas in both normal individuals and patients with gastric ulcer anacidity for one or more hours was common. The concentration of acid also manifested a definite diurnal and nocturnal rhythm. The concentration varied from hour to hour in the same individual. The values were usually highest between 7:30 p.m. and 2:30 a.m., and lowest during the early morning hours. In the normal and gastric ulcer groups

TABLE II

THE AVERAGE 12-HOUR NOCTURNAL GASTRIC SECRETION IN NORMAL INDIVIDUALS AND IN PATIENTS WITH ACTIVE UNCOMPLICATED DUODENAL ULCER BEFORE AND AFTER HEALING

	Volume (c.c.)	Free Acid (Cl. units)	Mg. Free HCl.
Normal	581	29	661
Active Uncomplicated Duodenal Ulcer	1047	58	2208
Healed Uncomplicated Duodenal Ulcer	1002	54	1957

periods of anacidity may be observed at any time throughout the 24 hour period, however, it occurred most often between 2:30 and 8:30 a.m.

The average hourly output of free hydrochloric acid was greatest in patients with duodenal ulcer. The values in normal individuals were significantly higher than in patients with gastric ulcer. In all subjects the rate of secretion varied from hour to hour in the same individual. In practically all patients with duodenal ulcer the output of hydrochloric acid exceeded 50 mg. per hour throughout the entire twenty-four hour period, and in more than half the duodenal ulcer series it consistently exceeded 100 mg. Persistent hypersecretion of this type was rarely encountered in normal individuals, and patients with benign gastric ulcer. Thus, patients with duodenal ulcer secrete free acid continuously throughout the day and night, and usually at a consistently higher rate. Under fasting conditions, in all three groups, the hourly output of acid was lowest between 5:30 and 11:30 a.m. After 11:30 a.m., the average hourly output of acid increased, the maximum amounts being secreted between 5:30 and 11:30 p.m. After 11:30

p.m., the output began gradually to diminish. This variation was observed in practically all of the individuals studied.

Comment

It is now generally accepted that the presence of acid gastric juice is indispensable to the formation of peptic ulcer. Approximately 4,000 patients with

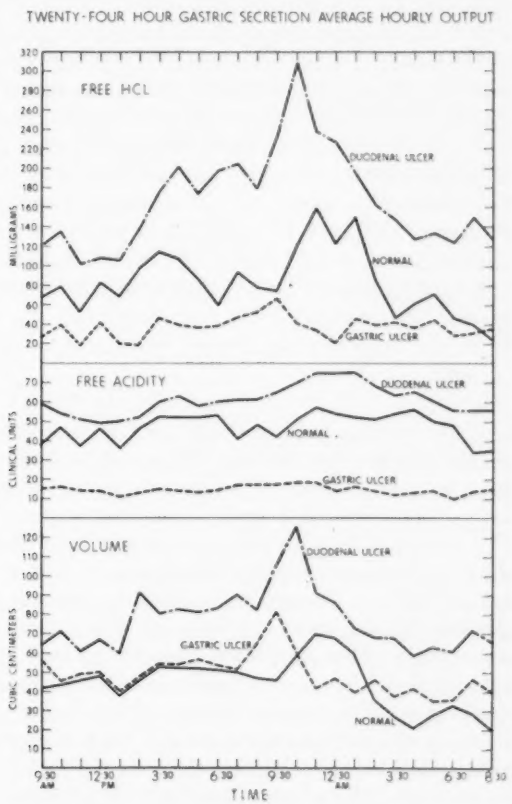

Fig. 2

duodenal ulcer and 750 patients with gastric ulcer have been seen at the University of Chicago Clinics since 1937. In no instance has a true achlorhydria been demonstrated. In 1940 Nutter and Palmer[5] analyzed the alleged instances of chronic ulcer with achlorhydria reported by others and found that none fulfilled the requirements stipulated by Palmer in 1926[6]. Subsequently, cases of peptic ulcer with achlorhydria have been reported; however, in our opinion the

evidence for peptic ulcer with achlorhydria was not satisfactory. This subject has been excellently commented upon by Grossman[7]. In certain instances of benign gastric ulcer, there may be marked fluctuations in gastric secretion. In some instances apparent achlorydria may be present[8]. However, in each case free acid is demonstrable in repeated histamine tests performed with careful technic.

Duodenal ulcer in rare instances and gastric ulcer very frequently occur in the presence of a low secretory response. It has been shown also that a normal individual may have a hypersecretion of acid and still have no ulcer. It is also well known that duodenal ulcer may heal spontaneously in spite of the presence of a high secretory rate. These observations, of course, do not negate the importance of acid gastric juice in the formation of peptic ulcer. It is recognized that other factors beside acid-pepsin are usually present, including lowered resistance of the gastric or duodenal mucosa to the acid attack. Palmer[9], in a recent study of patients with chronic gastric ulcer and a low secretion, showed that permanent healing of a chronic ulcer can be achieved when a true persistent achlorhydria is artificially induced by roentgen irradiation of the body and fundus of the stomach. This study clearly demonstrates that the presence of acid is indispensable to the formation of chronic ulcer even in patients secreting small amounts of acid.

In comparing the fasting secretory rate between normal individuals and patients with duodenal ulcer two distinct differences between the two groups are apparent. First, in approximately 80 per cent of patients with duodenal ulcer, the output of acid is definitely much greater than that obtained in normal individuals (Fig. 1). Secondly, in practically all patients with duodenal ulcer the secretion of acid is continuous; continuous secretion of acid is usually not observed in normal individuals. Consequently, the ulcer area not only comes in contact with relatively large quantities of acid, but does so continuously and for indefinite periods of time. This continuous secretion of acid in duodenal ulcer patients is maintained under fasting conditions indefinitely. Studies made in our laboratory for as long as 117 consecutive hours under fasting conditions show that this continuous acid secretion is maintained. This continuous secretion is usually maintained even after the ulcer is healed and the patient is free of symptoms. These findings have important therapeutic implications. Theoretically, the ideal treatment for peptic ulcer would consist of improving the normal protective mechanism of the gastric and duodenal mucosa from the destructive action of acid gastric juice, increasing tissue resistance of the ulcer bearing areas and by either neutralizing the acid gastric juice or by inhibiting the secretion of acid. At present, it is not possible to either influence the protective mechanism or to increase the tissue resistance of the ulcer bearing area. Similarly, we are unable by medical means to completely inhibit gastric secretion for prolonged periods. Atropine has been of questionable value[10]. Apparently, its chief value

in ulcer therapy is to delay gastric emptying, thus permitting a longer period of interaction between alkali and acid. Attempts have been made in recent years to develop more potent antisecretory drugs. Tetraethylammonium chloride and hexamethonium iodide may cause severe side effects. Banthine has achieved considerable popularity in the treatment of peptic ulcer. However, in our experience, the oral administration of Banthine in doses of 50 to 100 mg. does not effectively reduce the acid gastric secretion in patients with duodenal ulcer. Similar results have been obtained with several newer compounds such as Dibuline and Prantal. Consequently, until truly effective antisecretory agents are developed chief reliance must be placed on the use of antacids acting upon the gastric contents locally. It has been shown that any antacid is effective only as long as it is in the stomach where it can come directly in contact with the acid gastric juice[11]. The preceding studies on gastric secretion indicate that antacids not only must be given in sufficient quantities to neutralize the high acid content

TABLE III

AVERAGE 24-HOUR CONTINUOUS FASTING GASTRIC SECRETION

	Volume (c.c.)	Free Acid (Cl. units)	Total Output of HCl. (mg.)
Normal	1072	49	1900
Duodenal Ulcer	1950	57	4020
Gastric Ulcer	1048	22	922

but at frequent intervals throughout the day and at intervals during the night to provide adequate protection of the ulcer from the acid attack. Adequate antacid therapy must be maintained after healing of the original lesion, in order to prevent recurrences. The administration of alkali immediately after each meal or three or four times daily, as is commonly practiced, constitute inadequate antacid therapy. Numerous antacids have been recommended for various reasons; their efficiency has been recently reviewed[12]. In our experience the most effective preparation is calcium carbonate administered in doses 2 to 4 grams at hourly intervals alternating with hourly intake of milk and cream. Antacid therapy is continued after the ulcer heals and the patient becomes symptom free, the dosage and the schedule varying somewhat with the individual patient. Since it is obviously impractical to administer antacids throughout the night, atropine or Banthine may be prescribed at bedtime to prolong the emptying of the stomach and continue the antacid effect.

Approximately 10-20 per cent of patients with duodenal ulcer require surgical intervention for complications. The objective of surgery should be to cor-

rect the nature of the complication and to reduce the hypersecretion. In our opinion, the most physiological method to accomplish the latter is by vagotomy and gastroenterostomy. Dragstedt[12] has shown that vagus section will reduce the secretion in patients with duodenal ulcer to normal values. Unpublished data obtained by us demonstrate that vagotomy abolishes the continuous acid secretion in duodenal ulcer patients and that the secretory pattern reverts to normal. On physiological grounds, vagotomy is not indicated in patients with benign gastric ulcer, since gastric secretion either is normal or less than normal. When surgery is indicated, subtotal gastric resection is the procedure of choice for gastric ulcer.

It is interesting to note that patients with peptic ulcer very rarely complain of pain during the early morning hours (4:00 a.m. to 8:30 a.m.). In measuring the diurnal and nocturnal variation of gastric secretion, it was found that the secretion of acid is lowest during this period. Furthermore, ulcer pain most frequently occurs in the late afternoon, early evenings, and frequently awakes the patient between midnight and 2:00 a.m. It is during this period that the acid secretion is the greatest. Thus the relationship between acid and ulcer pain is further substantiated.

Summary and Conclusions

1. There are distinct differences between the basal gastric secretion of normal individuals, patients with duodenal ulcer and patients with benign gastric ulcer.

2. The secretion of acid in patients with duodenal ulcer is not only significantly greater than normal, but it is also continuous. In normal individuals the secretion of acid usually is intermittent.

3. Gastric secretion in patients with benign gastric ulcer is either the same or more often lower than normal.

4. Even though gastric ulcer may develop in individuals with a relatively low secretion of acid, abundance of evidence is available that acid is indispensable to ulcer formation.

5. The relationship between the basal secretion and adequate ulcer management is briefly discussed.

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Discussion

Dr. Rowland Ricketts (Merchantville, N. J.):—It is indeed a privilege to discuss this splendid paper, not only because it contains original work of a significant character, but also because the work has been applied clinically to a problem with which we are all familiar, and in a way which has been of benefit to patients and, I trust, to us. I might add right here that I did not have the opportunity of reviewing this work and of seeing these slides. If I had my discussion might have been somewhat different, but I do want to discuss the paper under two general headings.

First, a few comments on some of the specific remarks in the paper. I know that there was a publication on the result of roentgen irradiation of the stomach in 1948 by Dr. Palmer and Dr. Kirsner. I am, however, still interested in this roentgen achlorhydria, and in two ways. First I should like to ask Dr. Levin to tell me just what is the effect of roentgen irradiation upon the gastric mucosa. I mean by that the immediate effects; what actually happens to the mucosa? Is there a type of gastritis present or what is it that occurs?

I have seen from the slides that the change in many cases is reversible. The stomachs have been irradiated and acid has disappeared. In some cases acid has recurred, and they have been irradiated again. How often does Dr. Levin think that it is wise to irradiate the stomach?

Secondly, as to the remote effects; what happens in the long run to the gastric mucosa? What relationship, if any, has the author found in the applying of

a carcinogenic agent such as the roentgen-ray to an organ so prone to malignant degeneration as the stomach? I am vitally interested in that. I also wonder whether there were any changes in the blood picture.

I want to say here a few words about treatment. I believe that our treatment today is not adequate, and we have a very fine exhibit here which is an effort in the right direction to try to make it adequate. I think adequate treatment, however each of us defines it, must be maintained after the ulcer patient has become symptom free, and even after the ulcer has healed. It is characteristic of ulcer to recur and we cannot prevent recurrence unless we conceive of and give to the patient adequate treatment, *prolonged adequate treatment.*

Now I do not feel, however, that the question of adequate treatment is always a problem for which the physician is responsible. I feel that the patient is often at fault. One of the great criticisms of ulcer therapy so far as I am concerned is that within days or weeks the patient gets dramatic relief on almost any sensible type of ulcer therapy, and in many cases he disappears believing himself cured only to come back to you months later in a worse state than he was before.

We are obligated to discuss these facts and to explain them to our patients. I am sure that we do, and that we properly stress the condition. Nevertheless, patients continue to do as they please, and it doesn't make any difference how we treat their ulcer or how conscientious we are, we are not able to treat an ulcer when the patient doesn't bring it to us. I think we are often criticized unjustly. There is a doctor-patient relationship and if either half of that goes wrong, the treatment cannot be adequate.

I would urge that we individualize the treatment in this disease. You do not react to the things of this life as I do, and you would not react to your ulcer as I would to mine. We have got to keep in mind that there is a patient who has a disease, not a disease which has a patient, and that is why we sometimes do not get the results we expect out of routine treatment. We must apply to each what he or she needs.

I also want to say this—and before a gathering of this kind it may surprise you—but I often have to deal with the work of numerous medical men under varied conditions. I have been distressed by the number who are prescribing narcotics for the pain of peptic ulcer patients. I don't know whether any of you come across that or not. Please be on the alert for such a practice. It is more prevalent than you think. I have seen patients driven to addiction because of the persistence of some medical men in giving narcotics to quiet the pain of these patients. We all know that the intractable ulcer case can be a problem to the doctor, but that is part of our profession, and I do not feel that we should

get rid of that problem by giving narcotics and thereby creating a more serious one.

Now just a few words on the subject of vagotomy. As we saw by this paper, the effects of vagotomy are by no means definitely settled. The paper deals with the fact that vagotomy, as we heard yesterday, will abolish the continuous acid secretion in duodenal ulcer patients, but we have also seen that the secretory pattern after vagotomy may revert to subnormal or even to normal levels. We have also seen that small amounts of acid are all that we need sometimes to provoke or to keep an ulcer in a continuous state of activity. These facts may explain why it is that while vagus section does decrease the gastric secretion, there are in the literature papers by numerous, sincere, capable investigators which show that the acidity does return to normal after a period of time, that ulcer symptoms persist, actual ulcers recur, and, as we have seen today, even perforation takes place in vagotomized individuals. Orr and Johnson reported a series of 215 vagotomized cases in which 25 per cent had persistent symptoms or actual recurrence of the ulcer, and I think these figures and others like them are not to be denied nor their significance ignored.

Now, for the second heading of my discussion. There have been remarks made in this paper, and they are necessary I grant you, about gastric ulcer cases, duodenal ulcer cases, normal cases. I am not here to be facetious, but what is a normal individual, or who is a normal individual? The abdomen has been called the "Temple of Mystery," and certainly the stomach is one of the major shrines in that temple.

What is a normal stomach? The gastroscopists and all others concerned in this field are still trying to find that out. I know I often look into a stomach and see something which I have never seen before, and about which I have never read, and I wonder as I look: Is that normal, or if it isn't, what is it? I don't know. That is one reason why I am here, to find out.

What are the criteria upon which the definite designation of a normal stomach could or should be placed? What technic and interpretation of gastric analysis can we adopt whereby *all* investigators will accept the results and be guided by them, and so establish a common basis for the discussion of these problems?

The inability of various investigators to agree upon certain definite and specific factors in gastric work as well as in other phases of research holds us back. Just let me give you one example since we are pressed for time. There are several criteria for the determination of true achlorhydria. Many people will readily accept histamine, yes; but they cannot agree upon the dose. Some collect a specimen in forty-five minutes; others say that is incorrect, one should wait two hours; another group says there should be a double histamine meal, and one

very reputable investigator doesn't use histamine at all. He says it must be done with neutral red.

How are we going to reach a basis for discussion when there are such varied criteria existing for only one factor in the problem? Personally, I feel, as I get older in this work, that we know actually very little or nothing about the stomach. From this paper we could ask ourselves several questions which should convince us of the present state of our knowledge. These are not offered as criticisms but asked sincerely by a man doing exclusively clinical work in the hope that those of you who have the opportunity to do research may solve some of these problems in the near future.

Why does the stomach secrete as it does in the so-called normal, the gastric ulcer and the duodenal ulcer case? Are gastric and duodenal ulcers the same disease, or are they two entirely different diseases? Certainly the gastric response to each of them is totally different. If acid be one of the factors of causation of ulcer, why is there less acid in the gastric ulcer cases than in many so-called normal stomachs? One would expect the reverse to be true.

If acid and pepsin are the outstanding genetic factors in ulcer formation, why do we have, as a rule, one, clean-cut, punched-out ulcer in a rather specific location, when the entire gastric mucosa and some of the duodenum is bathed in this acid and highly peptic gastric juice? You would think that with digestion going on, the ulcer would not be clean-cut and punched-out but fairly ragged at the edges, but it isn't. We have all seen that, but we don't know why.

The French clinicians declare there is a neurovascularitis which devitalizes certain areas of the stomach and duodenum, and then they are digested, but they admit they have no idea as to what causes the neurovascularitis, and I wonder if any of us does.

So we might go on, and I repeat, there is very little actual irrefutable knowledge existing about the stomach which all research workers are willing to accept, and I think herein lies our opportunity as an organization which has international scope. We are in a position to do research among people of different climates, backgrounds, dietetic habits, etc., and such a procedure is certainly necessary. We are interested in research in this organization and here is a fertile field.

As I conclude I want to compliment the author on a fine paper wherein he has translated the tools of research into the tools of clinical usefulness, and I want to make a plea to this organization that we undertake carefully planned, carefully coordinated, long term research upon the stomach whereby we may

one day arrive at results acceptable to all, so that in the future we shall go forward together to the good of our profession, the improvement of our knowledge, and, above all, to the good of our patients.

Dr. Erwin Levin (Cleveland, Ohio):—Your Honorary President was the first one to give x-ray therapy, Dr. Bassler.

I want to thank Dr. Ricketts for his excellent discussion, and I should like to mention a few words about the use of radiation in peptic ulcer. Dr. Palmer and Dr. Kirsner started using x-ray as a means to attempt to decrease gastric secretion in 1938. Since 1938 there have been 1,040 cases so treated. I have had the privilege for the past seven years to work very closely with them in studying these cases, and the last year we started a study in which all these patients are now being contacted and follow-ups are made.

During the last year we had the opportunity of seeing approximately 600 of these cases. So far there hasn't been one case in which the x-ray caused malignant degeneration in the stomach. Now, there have been patients in this series who have died of carcinoma; however, the incidence of carcinoma in this group is not greater than the general population. There are two patients who were treated who died of carcinoma of the stomach; however, their deaths from carcinoma of the stomach occurred a year after their x-ray therapy. Their therapy was given for gastric ulcer and we are quite sure in our own minds that our diagnosis was wrong.

The immediate effect of x-ray on the stomach is to produce a superfiicial gastritis and then this might go in one of two ways: It might revert back to normal and, as we showed, the acid secretion comes back to pre-irradiation levels. In some cases, and unfortunately not in as many as we like, an atrophy occurs, and it is in these patients that the permanent achlorhydria results.

There has been no effect at all in these patients, on the blood picture. There are a couple of patients who have an anemia today, but this anemia can be very easily explained from the fact that they had subtotal gastric resections for duodenal ulcer, and a nutritional anemia resulted.

We think that x-ray therapy is not a cure for duodenal or gastric ulcer. It is another tool that can be used in an attempt by the physician to try to decrease the acid secretion which we sincerely believe is a very vital factor in the pathogenesis of peptic ulcer.

Now, just to digress a little bit and straighten out a few points as far as our method is concerned, these histamine tests that we have done on all these patients are fractionated analyses. The specimens are collected every ten minutes.

In every patient in whom an achlorhydria developed, we have given histamine continuously, by intramuscular injection and when we say an achlorhydria developed, it is a true achlorhydria. The pH of that gastric content does not become lower, even from a pH of 6 to a pH of 5, when histamine is given. It stays at the same level.

As to our normals, the normals were volunteers and, as Dr. Berger whispered, they were subjects who didn't even know they had a stomach. They were not patients in the hospital who had an organic disease; they were people I knew who worked around the hospital, friends of mine who came in and volunteered for these studies.

LIVER DISEASE AND LIVER LYMPH*

JAMES T. NIX, M.D.

New Orleans, La.

Observations on the flow and composition of liver lymph have been limited in number and significance by the rapid coagulation of lymph in cannulas designed for its collection. Recently, Cain and his coworkers[1] intubated the hepatic lymphatics of dogs with heparinized clot-resistant polyvinyl tubing, and reported the collection of lymph in large volumes over long periods. Their method has made feasible a broader study of liver lymph.

As the liver contributes the bulk of the fluid and protein content of thoracic duct lymph, and as a primary function of lymph appears to be the removal of excess blood protein from tissues, the protein pattern of hepatic lymph merits special interest. In this connection liver lymph is credited with a major role in plasma protein salvage, and the hepatic lymphatics are believed to be a conduit for both newly formed and stored protein. This investigation sought to explore the effect of liver injury on the protein profile and flow of liver lymph in the experimental animal.

1. Liver Lymph from Normal Dogs (Thirteen Dogs):—Preliminary to the study of liver lymph in liver disease, normal values for the concentration of protein fractions and the rate of flow of liver lymph were established[2]. Hepatic lymph contained 4.39 grams per cent of protein, 77 per cent of the average value for control plasma. Liver lymph had an albumin/globulin ratio slightly higher than that of control plasma and the rate of flow averaged 15 c.c. each hour. The liver contributed one-half the volume and two-thirds of the protein content of thoracic duct lymph. The volume of liver lymph in twenty-four hours was equivalent to 47 per cent of the estimated plasma volume and contained 35 per cent of the total circulating plasma proteins.

2. Liver Lymph from Dogs with Liver Injury, Experimentally Produced (Eight Dogs):—Five dogs with acute liver injury demonstrated that the gross appearance of liver lymph rapidly reflects changes in liver function. After liver biopsy (one dog) and cholecystectomy (one dog), lymph was bloody in a matter of minutes. After common duct obstruction (one dog) and a single exposure to carbon tetrachloride vapor (two dogs), there was a sudden and marked rise in the bilirubin content of liver lymph and plasma. No changes in lymph protein content or flow were manifested.

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*Read before the Sixteenth Annual Convention of the National Gastroenterological Association, Chicago, Ill., 17, 18, 19 September 1951.

Three dogs with extensive and irreversible liver damage best demonstrated the effect of liver disease on the protein profile and flow of liver lymph. In two of these dogs, the inferior vena cava was constricted above the diaphragm by a small band of cellophane. Six weeks later, both dogs showed massive ascites, hepatic congestion and varicose liver lymphatics the size of a lead pencil. Blood serum and liver lymph had a high globulin content and a low A/G ratio. These changes in protein constituency were accompanied by a 300 per cent acceleration in the volume flow and protein flow of liver lymph. In these dogs with hepatovenous congestion, the flow of liver lymph for twenty-four hours was equivalent to 128 per cent of the estimated plasma volume and contained the equivalent of 105 per cent of the total circulating plasma protein. The third dog with extensive liver damage had marked nodular cirrhosis with ascites and icterus after repeated exposure to carbon tetrachloride in an inhalation chamber. The flow of liver lymph for twenty-four hours was 258 per cent of the plasma volume and the protein content was 207 per cent of the circulating plasma protein—a 500 per cent acceleration in the rate of lymph flow. Furthermore, the flow of intestinal lymph was not increased in dogs with hepatovenous congestion or nodular cirrhosis.

Similar studies[3] on liver and cisternal lymph from our rats with nodular cirrhosis likewise showed liver lymphatic dilatation with lymphorrhea.

Comment

1. Liver lymph plays an important but unrecognized role in fluid and protein balance, liver function and disease.

2. Liver lymph in dogs with hepatovenous congestion and nodular cirrhosis flows through distended and varicose lymphatics at a markedly accelerated rate. The ascitic fluid in these animals closely resembles and may actually be liver lymph.

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EDITORIAL

Hiatus Hernia

Herniation of the stomach through the esophageal hiatus of the diaphragm is not uncommon, and is noted with increasing frequency as the average of patients examined progresses beyond 40 years. Some hiatus hernias may be asymptomatic; they may cause gastrointestinal symptoms; they may cause pain behind the sternum, in the precordium, in the upper back, neck, shoulder or arms, in the same distribution and with the same intensity as the pains of angina pectoris or myocardial infarction. Persons with severe attacks of pain from hiatus hernia seem to have the same paralysing fear that distinguishes angina pectoris and myocardial infarction, but the blood pressure is not lowered and the signs of shock do not persist beyond the duration of the pain. As a rule, attacks of severe pain due to esophageal hiatus hernia are not accompanied by fever, leucocytosis, or an increased erythrocyte sedimentation rate. The electrocardiogram may indicate cardiac hypertrophy, ventricular preponderance, and other more or less specific indications of cardiac involvement, but serial electrocardiograms will not show progressive changes characteristic of focal myocardial necrosis.

Differential diagnosis is essential between hiatus hernia and anginal pectoris, and can readily be done by utilizing the two-step exercise test of Master and the anoxemia test of Levy. These two tests will not bring on the pain or reveal the electrocardiographic changes significant of coronary disease.

Treatment of the hiatus hernia with diet and medication may relieve the symptoms temporarily. Should the attacks become frequent and unbearable, surgery may be needed even in the presence of true angina pectoris.

S. W.

CHAPTER ACTIVITIES

Boston Chapter

The Boston Chapter of the National Gastroenterological Association held a meeting at St. Elizabeth's Hospital in Boston, on Thursday, 17 January 1952.

The scientific session consisted of "Symposium on Early Diagnosis of Carcinoma of the Stomach". Dr. Wm. A. Carey presented "X-ray Characteristics of Gastric Carcinoma"; Dr. Stanley L. Robbins spoke on "Cytologic Studies in Gastric Carcinoma" and Dr. Henry M. Lemon discussed "Abnormal Electric Potentials in Gastric Disorders".

Dr. Frank H. Lahey will speak on "A Review of some of the Experiences of the Lahey Clinic with Lesions of the Alimentary Tract" at the meeting of the Chapter to be held on 26 March at the Boston City Hospital.

New Jersey Chapter

The New Jersey Chapter of the National Gastroenterological Association held a meeting at the Academy of Medicine in Newark, N. J., on 27 November 1951.

Dr. Joel Feldman, a new member of the Chapter presented interesting diagnostic gastrointestinal problems.

At the meeting held on 18 February 1952, Dr. E. Sciorsci of Hoboken, N. J. spoke on: "Carcinoma of the Gallbladder".

The Chapter voted to present an exhibit entitled "Gastroenterology in Everyday Practice" at the meeting of the New Jersey State Medical Society in Atlantic City in May.

New York Chapter

At the 5 November 1951 meeting of the New York Chapter, Dr. Asher Winkelstein presented the medical aspects; Dr. Louis Rousselot the surgical aspects and Dr. Maxwell H. Poppel presented the roentgenological aspects in a symposium on "Chronic Relapsing Pancreatitis".

Dr. Chas. B. Ripstein spoke on "Leimyosarcoma of the Gastrointestinal Tract" and Dr. Ralph Colp presented "Subtotal Gastrectomy with and without Vagotomy in Duodenal Ulcer" at the meeting on 14 January 1952.

The next meeting of the Chapter will be held at the New York Academy of Medicine on 10 March 1952. Dr. Ernest Gold will speak on "Postbulbar Duodenal Ulcer", Dr. I. Snapper on "Tropical Medicine in New York" and Dr. Anthony Bassler on "X-ray Treatment of Peptic Ulcer".

NEWS NOTES

Annual Meeting of the Executive Committee

The Annual Meeting of the Executive Committee of the National Gastroenterological Association was held at The Drake in Chicago on 16 September 1951.

Routine administrative matters were disposed of and reports of various committees and officers were presented.

The Cleveland, Grand Rapids, Milwaukee, New Jersey and New York Chapters presented for ratification the applications for membership of the following, which were approved by them and accepted by the Executive Committee: Dr. James P. Winkler, Cleveland, Ohio; Dr. F. A. Oldenburg, Cleveland, Ohio; Dr. Harold C. Klein, Cleveland Heights, Ohio; Dr. Austin B. Chinn, Cleveland, Ohio; Dr. Jac S. Geller, Cleveland, Ohio; Dr. Harold P. Roth, Shaker Heights, Ohio; Dr. Lester Wm. Krause, Cleveland, Ohio; Dr. Edward E. Woldman, Cleveland, Ohio; Dr. Fred C. Oldenburg, Cleveland, Ohio; Dr. Harman Albert Shecket, Shaker Heights, Ohio; Dr. Samuel Oscar Freedlander, Cleveland Heights, Ohio; Dr. James C. Droste, Grand Rapids, Mich.; Dr. James A. Ferguson, Grand Rapids, Mich.; Dr. Henry J. Van Duine, Grand Rapids, Mich.; Dr. Chas. Sherill Rife, Milwaukee, Wisc.; Dr. Robert T. McCarty, Milwaukee, Wisc.; Dr. Joel Feldman, Red Bank, N. J.; Dr. Henry G. Simmons, New York, N. Y. and Dr. Joseph S. Rechtschaffen, New York, N. Y.

The following were elected to membership at large in the National Gastroenterological Association: Dr. Wm. W. Weis, Piqua, Ohio; Dr. Gip R. Hudson, Kirksville, Mo.; Dr. Fred Michael Sheehan, Chicago, Ill.; Dr. Don M. LeDuc, Lansing, Mich.; Dr. Roger J. Minner, Allentown, Pa.; Dr. Francis Ruzic, Chicago, Ill.; Dr. Carlos Monteiro, Jackson Heights, N. Y.; Dr. Henry N. Powell, Colorado Springs, Colo.

Upon presentation of the necessary qualifications, the following were advanced as indicated: Dr. Benjamin M. Sakin, Brooklyn, N. Y., Associate Fellow; Dr. Francis B. Tabaka, Chicago, Ill., Associate Fellow; Dr. M. E. Gabor, Milwaukee, Wisc., Associate Fellow and Dr. Samuel Joseph Nigro, Chicago, Ill., Associate Fellow.

Annual Meeting of the National Council

The Annual Meeting of the National Council of the National Gastroenterological Association was held at The Drake in Chicago on 16 September 1951.

The Council heard reports from the various committee chairmen and ratified the actions of the Executive Committee meetings held during the interim of Council meetings.

By unanimous vote, Dr. I. Snapper, Director of Medical Education of The Mt. Sinai Hospital in New York and Dr. Abraham Ayala Gonzalez of Mexico City were elected to Honorary Fellowship in the National Gastroenterological Association.

Annual Meeting of the National Gastroenterological Association

The Annual Meeting of the National Gastroenterological Association was held at The Drake in Chicago, Ill. on 17 September 1951.

The President, Dr. Tidmarsh thanked the officers and members of the Executive Committe for their cooperation during the past year.

The committee chairmen made their several reports which were accepted as presented.

Dr. Lermann, reporting for the nominating commitee, advised that the slate of officers presented were the only candidates and moved the adoption of the committee's report. Upon motion duly made, seconded and carried the report was unanimously approved. Dr. Lermann then delivered the president's address and launched a membership campaign.

An amendment to the Constitution and By-laws, approved by the council, was submitted to the membership for ratification and was unanimously adopted.

Sixteenth Annual Convention

The Sixteenth Annual Convention of the National Gastroenterological Association which was held at The Drake in Chicago, 17, 18, 19 September 1951 saw the presentation of many informative and comprehensive papers delivered by eminent speakers from Chicago and elsewhere.

The cooperation of Dr. Sidney A. Portis, Dr. Andrew C. Ivy and Dr. Walter L. Palmer of Chicago with the program committee of the Association made this convention an outstanding medical meeting.

Papers and discussions presented are currently being published in The Review of Gastroenterology.

Convocation Ceremony

At the 1951 Convocation Ceremony in Chicago, a certificate of Honorary Fellowship was presented, in absentia, to Dr. Owen H. Wangensteen of Minneapolis, Minn., Co-chairman and Surgical Co-ordinator of the Course in Postgraduate Gastroenterology of the National Gastroenterological Association.

Dr. Wm. W. Lermann of Pittsburgh, Pa. presided at the ceremony and certificates were presented by Dr. C. J. Tidmarsh, of Montreal, Canada, who was President of the Association at that time.

Rabbi Norman E. Frimer, Dean of Students, Hebrew Theological College, Chicago, Ill. presented the invocation and the benediction was delivered by the Very Rev. John J. Clifford, S. J., President of the Pontifical Faculty, St. Mary's Seminary, Mundelein, Ill.

President's Reception

Through the kind cooperation of Winthrop-Stearns, Inc. members of the Association and guests at the convention in Chicago were invited to attend a reception to the outgoing President, Dr. C. J. Tidmarsh.

Annual Banquet

The Annual Banquet of the National Gastroenterological Association was held on Tuesday evening, 18 September 1951.

The speaker of the evening was Dr. Walter H. Judd, Member of Congress from Minnesota who discussed the Korean situation from a personal knowledge of the territory.

The judges for the 1951 Prize Award Contest reported that none of the entries had achieved the standards set for obtaining an award and consequently no prize was given for 1951.

Postgraduate Course

Immediately following the convention in Chicago, our Third Annual Course in Postgraduate Gastroenterology was presented under the Co-chairmanship of Drs. Owen H. Wangensteen of Minneapolis, Minn. and Dr. I. Snapper of New York, N. Y.

A distinguished faculty chosen from the Medical Schools in and around the Chicago area presented the Course and most of the papers and discussions will appear in subsequent issues of The Review of Gastroenterology.

Election of Officers

At the Annual Meeting of the National Gastroenterological Association held at The Drake, in Chicago, Ill., on Monday, 17 September 1951, the following officers of the Association were elected for the year 1951-52 as indicated: President-elect, Dr. Felix Cunha, San Francisco, Cal.; First Vice-President, Dr. Sigurd W. Johnsen, Passaic, N. J.; Second Vice-President, Dr. Lynn A. Ferguson,

Grand Rapids, Mich.; Third Vice-President, Dr. James T. Nix, New Orleans, La.; Fourth Vice-President, Dr. Arthur A. Kirchner, Los Angeles, Cal.; Secretary-General, Dr. Roy Upham, New York, N. Y.; Secretary, Dr. A. Xerxes Rossien, Kew Gardens, N. Y.; Treasurer, Dr. Elihu Katz, New York, N. Y.

For members of the National Council for a four-year term: Dr. Ludwig Frank, Charleston, W. Va.; Dr. Lester R. Whitaker, Portsmouth, N. H.; Dr. Bruce C. Lockwood, Detroit, Mich.; Dr. Harry M. Eberhard, Philadelphia, Pa., and Dr. Joseph Shaiken, Milwaukee, Wisc., were elected.

Dr. Yves Chaput of Montreal, Canada was elected to the unexpired term of the late Dr. Jean LeSage and Dr. I. R. Jankelson of Boston, Mass., was elected to fill the unexpired term of Dr. Nix who was elected Third Vice-President.

Dr. William W. Lermann, Pittsburgh, Pa. assumed the Presidency; Dr. C. J. Tidmarsh, Montreal, Canada was the outgoing President.

Executive Committee Meetings

Meetings of the Executive Committee of the National Gastroenterological Association were held in New York City on 28 October 1951 and 16 December 1951.

At the meeting on 28 October, after disposition of routine administrative affairs, the Boston, New York and New Jersey Chapters presented for ratification the applications of the following, which applications were approved by them and accepted by the Executive Committee: Dr. Timothy Dennehy, Boston, Mass.; Dr. Joseph H. Schwab, Woodhaven, N. Y.; Dr. George F. Simms, Lyndhurst, N. J.

The following were elected to membership at large in the National Gastroenterological Association: Dr. Ary Lopes de Almeida, Chicago, Ill.; Dr. Ezra J. Epstein, Sheboygan, Wisc.; Dr. Frank F. Fiore, Chicago, Ill.; Dr. Carl Norman Giere, Sacramento, Calif.; Dr. Joel W. Hardesty, Hannibal, Mo.; Dr. Raymond James Harrington, Sioux City, Iowa; Dr. Joseph L. Hrdina, Cicero, Ill.; Dr. Valdir Cordeiro Pessoa, Chicago, Ill.; Dr. Arthur E. Peterson, Greeley, Colo.; Dr. Glenn S. Rost, Lake City, Iowa; Dr. Rudy Ruhling, St. Louis, Mo.; Dr. Paul J. Shank, Dayton, Ohio; Dr. Henry A. Springer, Cincinnati, Ohio; Dr. Charles C. Teresi, Rochester, N. Y.; Dr. Warren D. Tuttle, Harrisburg, Ill.; Dr. George F. Wollgast, Denver, Colo. and Dr. William C. Wyte, Mt. Clemens, Mich.

The President, Dr. William W. Lermann, with the consent of the Executive Committee announced the appointment of the following standing committees:

Program Committee:—Dr. William W. Lermann, Pittsburgh, Pa., Chairman; Dr. C. J. Tidmarsh, Montreal, Canada; Dr. Sigurd W. Johnsen, Passaic, N. J.; Dr. Anthony Bassler, New York, N. Y.; Dr. Roy Upham, New York, N. Y. and Dr. Samuel Weiss, New York, N. Y.

Membership Committee: Dr. Bruce C. Lockwood, Detroit, Mich., Chairman; Dr. F. H. Voss, Phoenicia, N. Y.; Dr. H. E. DeWalt, Pittsburgh, Pa.; Dr. Lynn A. Ferguson, Grand Rapids, Mich. and Dr. Arthur Kirchner, Los Angeles, Calif.

Editorial and Publication Committee: Dr. Samuel Weiss, New York, N. Y., Chairman; Dr. Anthony Bassler, New York, N. Y.; Dr. Harry M. Eberhard, Philadelphia, Pa. and Dr. Wm. W. Lermann, Pittsburgh, Pa.

Endowment Fund Committee: Dr. William C. Jacobson, New York, N. Y., Chairman.

Convention Arrangements Committee: Dr. Samuel Weiss, New York, N. Y., Chairman and Dr. A. Xerxes Rossien, Kew Gardens, N. Y.

Nominating Committee: Dr. William W. Lermann, Pittsburgh, Pa., Chairman; Dr. Felix Cunha, San Francisco, Calif.; Dr. C. J. Tidmarsh, Montreal, Canada; Dr. E. A. Marshall, Cleveland, Ohio and Dr. G. Randolph Manning, New York, N. Y.

The Research and Postgraduate Education Committees were not appointed at this time.

A special committee on publicity was appointed with Dr. Lynn A. Ferguson, Grand Rapids, Mich., Chairman and the other members Dr. Arthur Kirchner, Los Angeles, Calif.; Dr. Roy Upham, New York, N. Y. and Dr. G. Randolph Manning, New York, N. Y.

The Executive Committee voted to again invite Drs. Owen H. Wangensteen and I. Snapper to be Co-chairmen and Surgical and Medical Co-ordinators respectively for the 1952 Course in Postgraduate Gastroenterology.

The committee voted to continue annual dues for 1952 at the rate set for 1951.

At the meeting of the committee held on 16 December an acceptance for the Postgraduate Course was received from Dr. Snapper.

Dr. Roy Upham, Secretary-General reported on the meetings of the Boston and New Jersey Chapters.

The New York Chapter presented for ratification the application of Dr. Mortimer Lefkowitz, Brooklyn, N. Y., which application had been approved by them and was now accepted by the Executive Committee.

Dr. C. Wilmer Wirts of Philadelphia, Pa. was elected to membership at large in the National Gastroenterological Association.

The Editor, Dr. Samuel Weiss, presented a financial statement for THE REVIEW OF GASTROENTEROLOGY.

Dr. Lermann, reporting for the Program Committee reported progress on the tentative program for 1952.

A membership brochure was submitted to the committee for approval and its printing and distribution was authorized.

SEMI-ANNUAL MEETING OF THE NATIONAL COUNCIL

The Semi-Annual Meeting of the National Council of the National Gastroenterological Association will be held at the Hotel Statler in New York City immediately following the regular scheduled meeting of the Executive Committee, on Sunday, 16 March 1952.

The meeting will hear reports of the various committee chairmen as well as the reports of the Executive Committee meetings held since the Annual Meeting of the Council.

Members of the Council from all parts of the country are expected to attend.

SEVENTEENTH ANNUAL CONVENTION

The Seventeenth Annual Convention of the National Gastroenterological Association will be held at the Hotel Statler in New York City on 20, 21, 22 October 1952.

The Program Committee, consisting of Dr. William W. Lermann, Pittsburgh, Pa., chairman; Dr. C. J. Tidmarsh, Montreal, Canada; Dr. Sigurd W. Johnsen, Passaic, N. J.; Dr. Anthony Bassler, New York, N. Y.; Dr. Roy Upham, New York, N. Y. and Dr. Samuel Weiss, New York, N. Y., are planning a comprehensive and instructive scientific session.

A feature of the meeting will be a "Symposium on Gastroenterology for the General Practitioner" to be given on Tuesday morning, 21 October 1952.

Also planned is a panel discussion on Gastrointestinal X-ray for Wednesday afternoon, 22 October 1952.

The meeting will be open to members of the medical profession whether or not affiliated with the National Gastroenterological Association.

Course in Postgraduate Gastroenterology

The Fourth Annual Course in Postgraduate Gastroenterology sponsored by the National Gastroenterological Association will be given in New York City on 23, 24, 25 October 1952, immediately following the Seventeenth Annual Convention.

The Association is again fortunate in having Dr. Owen H. Wangensteen, Professor of Surgery and Chairman of the Department of the University of Minnesota Medical School as Co-chairman and Surgical Co-ordinator, and Dr. I. Snapper, Director of Medical Education, The Mt. Sinai Hospital of New York as Co-chairman and Medical Co-ordinator.

This year the Course will include a series of lectures by an outstanding faculty selected from the facultys of the medical schools in and around the New York area as well as a clinical session at one of the leading hospitals in the city.

Preliminary announcements and application blanks for the Course will be mailed about the first week in May.

The fee for the 3 days will be $50.00 for non-members of the Association and $35.00 for members of the Association.

A copy of the premlinary announcement and application blank may be obtained by writing Dept. R.G., National Gastroenterological Association, 1819 Broadway, New York 23, N. Y.

In Memoriam

We record with profound sorrow the passing of Mrs. Anthony Bassler, wife of our Honorary President, Dr. Anthony Bassler; Dr. Franz Groedel, Associate Fellow, New York, N. Y.; Dr. Welman B. Christie, Associate Fellow, Boston, Mass. and Dr. William Ackerman, Member, Milwaukee, Wisc.

Our deepest sympathies to the bereaved families.

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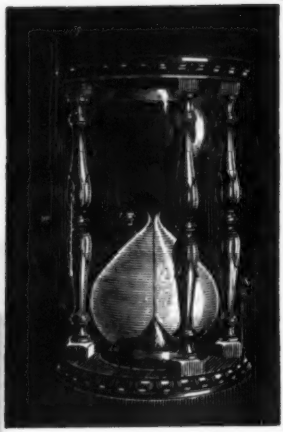

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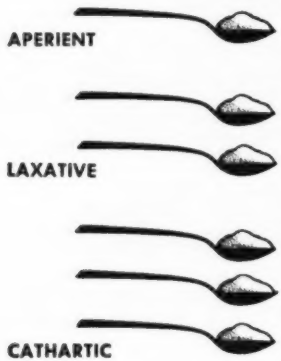

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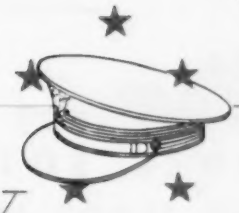

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1. Best, C. H.; Lucas, C. C.; Patterson, J. M., and Ridout, J. H.: Lipotropic Properties of Inositol, Science *103*:12 (Jan. 4) 1946.

2. Dolan, R. A.: Choline and other Lipotropic Factors: Mechanisms of Action and Significance in Chronic Liver Disease, Minnesota Med. *31*: 1198 (Nov.) 1948.

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4. Cogswell, R. C.; Schiff, L.; Safdi, S. A.; Riehfield, D. F.; Kumpe, C. W., and Gall, E. A.: Needle Biopsy of the Liver, J.A.M.A. *140*:385 (May 28) 1949.

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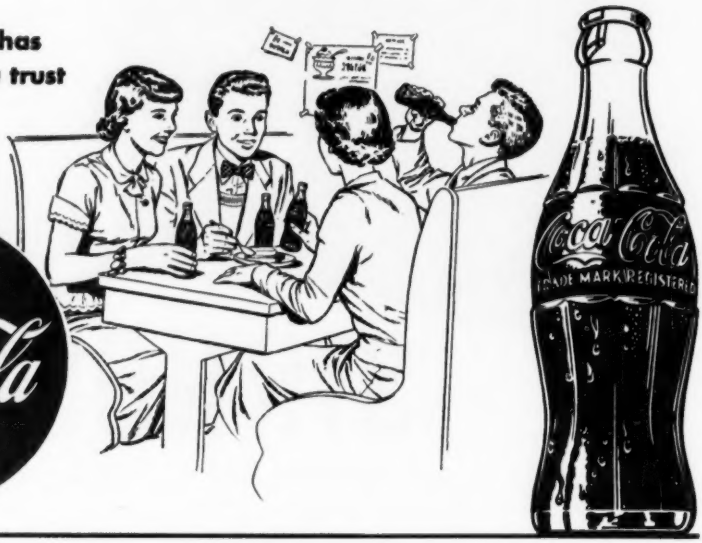

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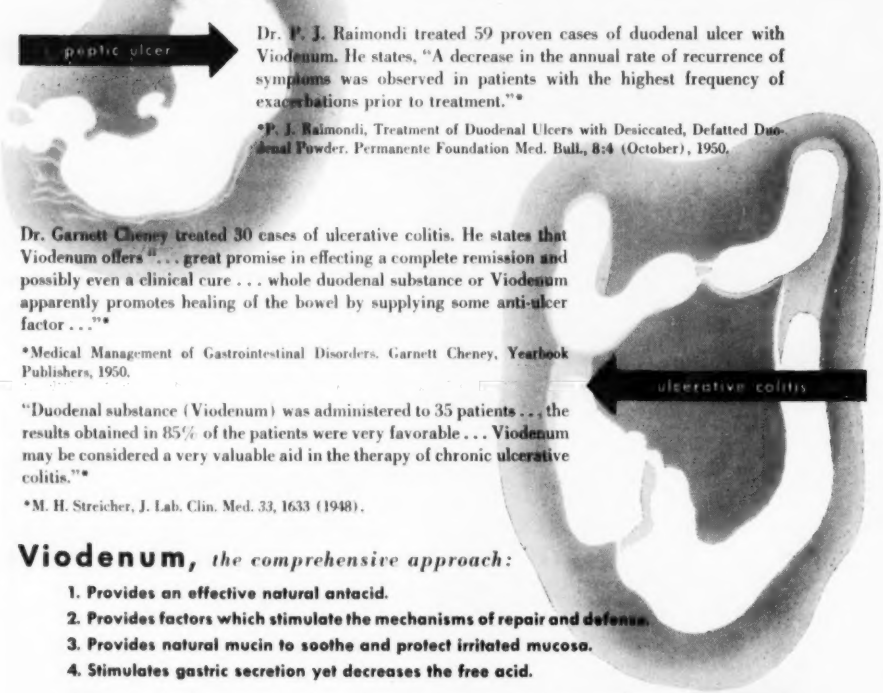
*S. Krasnow, F. Steigmann and L. L. Hardt, Comparison of Effectiveness of Various Antacids on Gastric Acidity. Am. J. Dig. Dis., 17:242 (1950).



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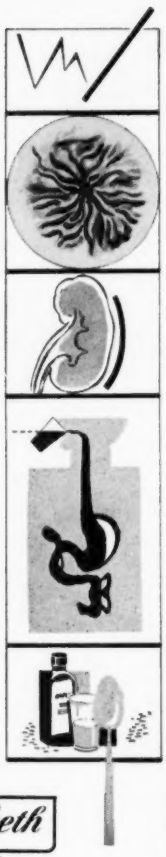

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